BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 12 1960

STAPHYLOCOCCAL INFECTION: ANTITOXIC IMMUNITY*

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This difficult topic may fittingly be introduced by a brief consideration of the role of antitoxic immunity in various infections other than staphylococcal. In diphtheria and tetanus the presence of antitoxin in sufficient quantity at the right time in the circulating blood is synonymous with immunity. In scarlet fever also—fortunately now a rare infection—antitoxin is of value in preventing the rash due to streptococcal toxin, and in causing it to disappear rapidly if it is already present at the time of administration. However, in other streptococcal diseases, in the era before effective chemotherapy was introduced, antitoxic serum was tried as soon as it was realized that the erythrogenic toxins of the haemolytic streptococci were for practical purposes identical (Okell and Parish, 1928; Okell, 1932); the small number of qualitative variations to which attention was subsequently directed has not invalidated the main thesis.

Results in treatment were conflicting at first because they rested on clinical impressions and not on any more certain means of scientific assessment. In retrospect, streptococcus antitoxin was certainly useful in a few cases of sepsis with a scarlatiniform rash, but in the ordinary run of puerperal infection, erysipelas, and general septicaemia the final verdict was that it was valueless—and that in spite of the laboratory evidence that antitoxic serum delayed the death of rabbits injected intravenously with large doses of living haemolytic streptococci from these conditions. As there was apparently no protection against virulent strains of streptococcus, the neutralization of the specific erythrogenic toxin was not a complete answer to the problem of streptococcal invasion.

Many of the toxic products of staphylococcal filtrates had been studied, mostly by German workers in the decade before 1905, but this early knowledge was largely neglected for nearly a quarter of a century. In 1928, a few years after the corresponding and in some respects similar investigation of haemolytic streptococcus toxins, research was resumed (Burnet, 1929, 1930, 1931): it had received a fresh impetus from the immunization disaster at Bundaberg, in Queensland, Australia, where 12 out of 21 children died from overwhelming staphylococcal toxaemia within 34 hours of receiving an injection of contaminated diphtheria prophylactic to which no preservative had been added.

A further incentive to research was derived from the analogy between staphylococcus alpha toxin and diphtheria, tetanus, and haemolytic streptococcus toxins, and also the ease with which this toxin and its corresponding antibody can be demonstrated and measured with accuracy. It was fitting to inquire how far the experimental findings in rabbits, guinea-pigs, and mice, in which the neutralization of toxin has a demonstrably beneficial effect, could be applied to the prophylaxis and treatment of staphylococcal disease. Notwithstanding the failure with a streptococcus antitoxin to prevent streptococcal invasion in man, there was considerable optimism that, even if all toxins and other factors in the attack of the staphylococcus were not combated directly, once the potentially dangerous alpha toxin was out of the way the body's defences would be enabled to deal with the others.

In this communication it is impossible to survey the considerable literature of toxin, toxoid, and antitoxin: this has been admirably carried out by Elek (1959). Our purpose is to indicate in the space at our disposal what has been achieved and also the gaps in our knowledge necessitating further basic work. As a background to this task, we propose to deal with some of the experimental findings and the views expressed in various published articles and personal correspondence over three decades.

The gravity of staphylococcal septicaemia (excluding the irregular bacteriaemia of osteomyelitis, etc.) was much discussed in 1928 at the time of the Bundaberg disaster, which was the starting-point of Burnet's work on the alpha toxin and is therefore of special relevance to this review. The following data have been abstracted from the early literature:

Staphylococcus Septicaemia

	No. of Cases	Mortality
Otten (1907)	55	80%
Soper (1912)	40	72%
Jochmann (1924)	23	95·6%
Bundaberg (Queensland) disaster in 1928	21	57%
Lowenstein (1931)	57	61·4%

Thus, true staphylococcal septicaemia had a case-fatality of the order of 60 to 95%.

Staphylococcus Alpha Toxin

The method developed for preparing staphylococcus toxin at the Wellcome Research Laboratories (Parish and Clark, 1932) was one of several variations of the

*Based on a paper read by one of us (H. J. P.) at the Symposium on "The Staphylococcus" at the Postgraduate Medical School, Hammersmith, July, 1959.

procedure introduced by Burnet (1929, 1930), and may be summarized as follows:

The "Wood 46" strain is employed, as has been customary in most serological laboratories. Isolated in Australia from extensive infected burns, this is a consistently high producer of alpha toxin, analogous in its reputation to the "Park William 8" strain in the production of diphtheria toxin. The culture medium is 0.8% ("sloppy") agar under 25% CO_2. After 48 hours' incubation, modified Parker's broth is added: this contains 4% Witte peptone or Difco proteose peptone. The bottles are shaken to break up the agar. After a further period of incubation for four days under 25% CO_2, the cultures are harvested: the filtrate contains the alpha toxin.

Tasman *et al.* (1952) and Tasman and van der Slot (1953) have investigated and modified this method at the National Institute for Public Health, Utrecht. While confirming that CO_2 is indispensable, they obtained better results with a softer agar—0.5% instead of 0.8%. Their experiments suggested that the addition of Parker's broth in the second phase of the preparation was unnecessary. It was first replaced by 3% casamino acids, and later by normal saline, which was an equally effective extractive at lower cost and with a lower nitrogen content. This ensured greater purity of the product, apparently without any loss of stability, and facilitated further purification.

Many other types of media and procedure are reviewed by Elek (1959).

Staphylococcus Toxoid: Preparation and Purification

At the Wellcome Research Laboratories the alpha toxin is treated with 0.2% formaldehyde for 10 days at 37° C. Tasman and van der Slot (1953) found that the alpha toxin which they extracted from soft agar with saline detoxified a little more quickly than when extracted with broth or casamino acids. Toxoids prepared by either method are very stable.

Since the toxoids used originally were impure preparations and caused reactions, various attempts were made to improve them by purification. Holt (1936) salted out with ammonium sulphate and obtained an 80 to 90% yield. Burnet and Freeman (1932) tried precipitation with acetic acid, and Boivin and Izard (1937) precipitation with trichloracetic acid. Wittler and Pillemer (1948) used fractional precipitation in methanol–water mixtures at accurately controlled temperature (below freezing-point), *p*H, and ionic strength. Tasman *et al.* (1952) employed ultrafiltration and rejected acid precipitation since it damaged the antigen. Tasman, in a personal communication in 1959, informed us that he has been using ultrafiltration and salting-out with ammonium sulphate for about two years. The toxoid is adsorbed on to aluminium sulphate (10 Lf and 3 mg. $AlPO_4$ per ml.). Much has been achieved by these modifications, because Tasman states that his ultrafiltered and adsorbed preparation produces *no unpleasant reactions*. Work on purified toxoid is in progress in other laboratories also, and more potent and milder preparations can now be investigated clinically than were available in the 1930s.

Antitoxic Immunity in Animal Experiments

Alpha toxin kills rabbits, guinea-pigs, and mice rapidly on intravenous injection; it produces necrotic lesions on intradermal injection into rabbits and guinea-pigs; it has a haemolytic activity for rabbit red blood cells proportional to its toxicity; and it has a destructive action on rabbit leucocytes, but practically none on human leucocytes. It has to be differentiated from the true leucocidin (Panton and Valentine, 1932; Valentine, 1936), which is destructive for both human and rabbit leucocytes but without action on red cells.

Alpha antitoxin (horse, rabbit, or human) has protective properties which can be investigated by (*a*) a rabbit intravenous method, (*b*) a skin-neutralization method (guinea-pig), and (*c*) the titration of anti-haemolytic properties. The measurement of staphylococcus antibody by a mouse-protection test is being reinvestigated by Fisher (1959).

As the alpha antibody is present in the pseudo-globulin fraction of the serum, it has been found possible to concentrate horse antitoxin by the usual method of pepsin treatment.

The immunization of rabbits or horses with toxoid or toxin produces high titres of circulating antitoxin. When immunized rabbits are challenged by intradermal or subcutaneous injection of virulent culture, the resulting lesions show a minimum amount of necrosis, are less extensive, and heal more rapidly than those produced in controls. Immunized animals also outlive controls on intravenous challenge with a lethal intravenous dose, but sterilization of the tissues is not consistently obtained and metastatic abscesses ultimately develop in the viscera or joints. The immunity is antitoxic rather than antibacterial. We have already indicated the close analogy here between the value of staphylococcus antitoxin and streptococcus antitoxin in protection experiments in rabbits; streptococcus antitoxin also neutralizes the toxin in living broth cultures of toxigenic haemolytic streptococci, but while the lives of the "protected" animals are prolonged they almost all develop streptococcal arthritis, with pus in or around one or more joints (Parish and Okell, 1927): the serum is deficient in antibacterial properties. Thus, in both streptococcal and staphylococcal infections, humoral antibody is not the whole story, and something else, of which we have scarcely an inkling, is needed to dispose of the invader.

Downie (1937) failed to demonstrate any immunity in response to suspensions of *washed* heat-killed staphylococci: animals so injected reacted like the normal controls when challenged with toxin or living organisms; washed vaccines may therefore have lost important protective antigens in the washings. Perhaps when formolized and other "whole" vaccines give rise to some immunity in man, at least one factor may be alpha toxin or toxoid or both in their supernatant, which would stimulate the production of alpha antitoxin on injection. However, a rise in antitoxin titre does not ordinarily follow treatment of animals or patients with staphylococcus vaccines, and, in general, vaccines have been regarded as inferior to toxoids as immunizing agents (Kitching and Farrell, 1936).

Antitoxic Immunity in Man

The results obtained with staphylococcus toxoid and antitoxin in animal experiments have been paralleled to a limited extent in the prevention or treatment of human disease, but antitoxic immunity appears to be even less important in man than in the rabbit. As Elek (1959) points out, the alpha toxin is a leucocidin to the

rabbit, which may explain why this species may derive certain advantages from antitoxin which are denied to man.

In examining the problem the following question may be postulated. What is the relationship (if any) between circulating alpha antitoxin and clinical protection? How good are the results with toxoid and antitoxin in man, and could they be improved by the use of purer and more potent antigens, perhaps with some adjuvant? Relatively poor toxoids may have been used for immunization procedures in early investigations (Glenny and Stevens, 1935). A purified alpha toxoid would be less likely than crude toxoid to cause reactions in man, and also in horses undergoing immunization for the production of antitoxic serum; after purification, antigens would be more acceptable, could be used in larger doses if necessary, and should lead to better sera. What consideration should be given to antigens other than the alpha toxoid? Would better results be obtained by using different toxoids for immunization, or perhaps by mixing these antigens with some other constituents—possibly by combining toxoid and vaccine? Would the extra effort be justified on the evidence? We feel that we have only partial answers to these questions.

The wide range of values of *circulating antitoxin* within groups classified as "normal" humans and in groups of the various staphylococcal diseases is noteworthy. It is impossible to give a baseline or even a zone for normality and therefore to state what constitutes an abnormal finding. In general, patients with boils, blepharitis, acne, sycosis, and other superficial infections give values which are practically unaltered or only slightly above normal: the absence of any regular increase suggests that antitoxin is not an important factor in immunity. The values in cases of carbuncles, acute osteomyelitis, and purulent arthritis may be slightly or moderately raised, but here again the values do not correlate with the course of the disease. With chronic osteomyelitis, perinephritic abscess, pyaemia—what have been termed "deep-seated infections of bone and muscle"—the titres may be very high, though not always so. Low titres do not necessarily indicate inability of the patient to produce antibody, as many such patients respond well to toxoid.

Toxoid in Superficial Infections

In the early years of toxoid, much of the clinical investigation was carried out by clinical pathologists who were impressed by the considerable increase in anti-alpha-haemolysin titres—the haemolytic method of titration was employed—and by the concomitant recovery or remission from staphylococcal lesions, in the majority of subacute or chronic cutaneous infections. Some dermatologists who had long experience of the behaviour of various types of superficial lesion tended to be less enthusiastic, and thought that equally good results had often resulted from the non-specific measures in vogue at that time. Discrepancies appeared at once. Rises in circulating anti-haemolysin titres in response to toxoid were usual but by no means invariable; there was, in fact, no definite level of antitoxin which could be taken to demarcate a successful result from failure. It was difficult to understand why some patients with intractable furunculosis might have "normal" values of circulating staphylococcus antitoxin and yet have a history of remissions, the mechanism of which was obscure from the immunological standpoint. Clinicians, whose impressions were unfavourable to toxoid, were hesitant about publication, and their adverse comments seldom appeared in the literature. The controversy about the role of antitoxic immunity was still unsettled when chemotherapy made the topic unimportant but of rather academic interest.

One of us (H. J. P.) formed the impression that the toxoid used in the 1930s was often helpful, perhaps in 70% of cases. Some of the reports he received were impressive, and in a limited personal experience his successes outnumbered the failures: unfortunately, attempts to arrange controlled trials were abortive. The case of one woman, herself a well-known research worker in this field comes to mind. She had a history of recurrent carbuncles when she received a long course of toxoid with apparent success. Disappointment ensued when a further lesion developed; but fortunately, to her astonishment, a single small injection of toxoid cured it overnight. On two or three subsequent occasions, at intervals of several months, abscesses or carbuncles were kept at bay by these reinforcing doses given early in attacks. This impressive experience has not been unique, and it has been stated by protagonists of toxoid that recurrences after a course are usually milder and tend to respond rapidly to further injections.

Over a period of 10 years Ramon *et al.* (1946) recorded failure in only about 7% of approximately 3,000 cases of cutaneous infections treated with toxoid.

Belatedly, and as recently as 1951, Macdonald and Taylor were able to arrange a controlled clinical trial of toxoid on young R.A.F. personnel with pustular acne. Of 34 cases treated with toxoid, 21 (62%) showed improvement, whereas in the control group of 32 cases treated with broth, only 5 (16%) improved.

Toxoid in Deep-seated Infections

Since antitoxic immunity is, at best, only one aspect of defence against staphylococci, it is hardly surprising that the results obtained with toxoid in deep-seated infections, such as chronic osteomyelitis, have been uniformly disappointing (Blair, 1937). As already mentioned, the values of circulating alpha antitoxin in many cases of osteomyelitis are already unusually high, and further variations after the injection of toxoid do not correlate with the course of the disease.

Antitoxin in Treatment

The value of antitoxin therapy was subjected to the same controversy as toxoid: there is a considerable literature (Elek, 1959). Our views coincide with those of Blair (1958), as follows: "Staphylococcal antitoxin has a definite but restricted role, which is properly confined to fulminating systemic infections, especially in children, with evidence of severe toxaemia (Kleiger and Blair, 1943). When administered intravenously early and in adequate doses, antitoxin may carry the patient over the acute period of emergency. Upon survival of the acute phase of the infection, the clinical picture becomes chiefly that of the effects of metastases to various tissues or organs. Antitoxin therapy in this phase is of little value, nor can it be expected to influence an infection due to a non-toxigenic strain."

The difficulties and pitfalls inherent in any attempt to influence staphylococcal infections by specific measures are illustrated once again by the above quotation. What are some of the gaps in our knowledge left by previous neglect, and what research projects might be undertaken to fill them?

Criticism and Suggestions

In the preparation of antigens the selection of polyvalent strains might be rewarding. Hitherto too much attention may have been given to the "Wood 46" strain, and therefore to the alpha toxoid or haemolysin it produces. It is not known whether better results would be obtained if, in addition to the alpha toxoid, beta and possibly gamma and delta toxoids were included, and also strains of staphylococci—or preferably one autogenous strain—in other words, if, together with a more comprehensive antitoxic immunity, some antibacterial immunity were sought as well. The antigenicity of the specific coagulase should be considered in the selection of strains. More attention, too, might be paid to the anti-leucocidin for human leucocytes, as suggested by Panton and Valentine (1932) and Valentine (1936). The enterotoxin which is associated with staphylococcal food-poisoning is different from these other toxins and does not appear to be antigenic.

Dolman (personal communication, 1959) considers that "strains of staphylococci currently prevalent in hospital 'reservoirs' . . . might elaborate labile or elusive antigens (leucocidins, for instance) which could be very important. In any event such antigens are unlikely to be present in the monovalent alpha toxoid now being manufactured, as the 'Wood' strain has been through many subcultures since its first isolation 30 or so years ago. In the early days, the Connaught Laboratories' toxoids were made from the pooled filtrates of some six to ten strains, which included always one or two freshly isolated ones. The results obtained from these polyvalent antigens were certainly better than those given by the monovalent product. Of course the earlier toxoid was much harder to make and standardize; and introduction of the standard unit of alpha-antitoxin encouraged the use of material of single-strain origin. For some time I have been trying out, under Connaught Laboratories' auspices, a bivalent toxoid, in which both alpha and beta toxoids are present in known proportions. The clinical results have been encouraging in some cases of recurrent infection which proved intractable to alpha toxoid and antibiotics. But I feel that even the bivalent toxoid does not measure up to the 1932–5 results in Toronto—either because nowadays the flora is more versatile, or because the antigens are less comprehensive."

Mercier (personal communication, 1959) also favours the use of a multiplicity of antigens. He makes the interesting suggestion that antibiotic therapy should always be accompanied by the most complete immunization possible—namely, heat-killed staphylococci of the Cowan types most frequently found in the area, suspended in purified toxoid. As the immunity is transitory, frequent boosting doses are necessary.

Murray (personal communication, 1959) is still an enthusiastic user of toxoid, either alone or as a constituent of vaccines ("vaccoids").

It follows from the brief review in earlier sections of this article that the medium used for toxin production and the rationale of growth could be improved by the type of intensive study which has proved so fruitful in the production of, say, diphtheria toxin or pertussis vaccine. Further, a purified toxoid would reduce the incidence of untoward reactions, permit larger dosage and fewer injections, and induce better antibody response. Considerable work on adjuvants is also indicated.

Some of the poor results with toxoid have been ascribed to weak or otherwise unsatisfactory preparations. It has been suggested that, by analogy, the control of diphtheria and whooping-cough would have been failures if only weak antigens had been available. Alternative explanations have also been advanced—for example, Branch (1938) felt that once a focus of infection had become established toxoid gave no protection. Elek (1959) makes the acid comment that "the old clinical maxim has been applied to toxoid treatment: 'Useful in carefully selected cases.' It should be added, however, that the selection has usually had to be made in retrospect."

Attention has been drawn by Stuart-Harris (1959) and others to the importance of the staphylococcus in cases of pneumonia complicating the epidemic of Asian influenza of 1958. This organism was found in 62% of the British and 67% of the Dutch necropsies. Resistance to penicillin was common. There was no evidence of bacteriaemia. Often death appeared to be due to the toxic effects of the infection. Though antibiotics are of course useless for the bacterial toxaemia of these complicated cases, Stuart-Harris concluded that staphylococcus antitoxin had not "really justified its claim for inclusion in the therapeutic regime."

Dolman (1956) has mentioned some errors and difficulties in the administration of antitoxin and in assessing the results. While antitoxin had been valuable in severe and even desperate acute cases in Montreal (Dolman, 1934), some doctors appeared to expect small doses to cure patients riddled with abscesses, perhaps in sites inaccessible to circulating antitoxin. In other cases large doses were given in the late stages of the infection when damage was already irreparable. More recently, Dolman (personal communication, 1959) has not lost his early conviction that "toxins of one sort or another play a big part in the pathogenic activities of staphylococci. . . . If antitoxin were used earlier in larger intravenous doses, it would be very useful, particularly in the fulminating bronchopneumonia and enterocolitis cases which are so baffling to cope with otherwise." Dolman deplores once again that, though antitoxin is used in many hospitals in Canada, it is given only on rare occasions: "presumably the evidence of 'toxaemia' is overwhelming in fulminating cases, and when a patient is at death's door there is willingness to try out anything that sounds 'specific.'"

Murray (1935; personal communication, 1959) agrees with Dolman that antitoxin, given quickly enough with or without an antibiotic, is often valuable in acute infections.

A rare staphylococcal "scarlet fever" has been described: possibly the rash is due to a toxin which might be controlled by antitoxic serum. Essential information is lacking (Negro *et al.*, 1956).

Gamma-globulin.—Ede *et al.* (1959) used gamma-globulin in critically ill cases of staphylococcal pneumonia, but were unable to judge its *real* efficacy because other agents were being given at the same time.

Allergy.—While repeated injections of living cultures of staphylococcus will immunize rabbits, they will at the same time cause hypersensitivity to small doses which have no effect on normal animals (Panton and Valentine, 1929); thus immunity may coexist with hypersensitivity in staphylococcal as in other infective conditions.

Though several papers have been published on the part played by allergy in staphylococcal infections (Elek, 1959), nothing of practical value has so far emerged from experiments involving allergy. This line of investigation is unpromising.

Conclusion

Antitoxic immunity is only one factor in the control of infection generally. There is a close parallel between staphylococcus antitoxin and haemolytic streptococcus (scarlet fever) antitoxin in that both protect rabbits against intravenous lethal doses of culture without disposing of all the invaders: temporary recovery from the inoculation is followed by abscess formation (metastases) in various sites.

In man, also, staphylococcal and streptococcal infections may persist in spite of procedures designed to raise the concentration of serum antibodies to the highest possible level. Nevertheless, there is evidence, which appears adequate, that staphylococcus antitoxin will prevent some fatalities from staphylococcal infection in human subjects, and that the administration of alpha toxoid may be useful in many cases of superficial infection.

Suggestions have been made in this paper for "improving" antigens and antibodies in various ways. But humoral immunity is not the full story: there is an elusive "something else," and the study of staphylococcal infection—and indeed of infection generally—"will have taken a great step forward when the nature of this other factor is brought to light" (*Brit. med. J.*, 1937).

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OBSERVATIONS ON 100 CASES OF LEUKAEMIA IN CHILDHOOD

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[WITH SPECIAL PLATE]

Deaths attributed to leukaemia at all ages in England and Wales have increased two and a half times in the last two decades (Registrar-General's Statistical Review, 1938–57). In childhood there is now a peak incidence between the ages of 2 and 4 years (Hewitt, 1955). Acute leukaemia accounts for nearly 25% of cases of malignant disease admitted to the Hospital for Sick Children, Great Ormond Street. In this paper a survey of clinical and radiological findings is presented and an analysis made of the form and duration of remissions induced by antileukaemic agents. Steroids are prominent in treatment, and the place of antimetabolites has been firmly established since the original studies of Farber *et al.* (1948) on folic-acid antagonists and of Burchenal *et al.* (1953) on 6-mercaptopurine. Remission therapy can lengthen life and can change the clinical course of the disease. It can also affect pathology; references to infiltration of the kidneys (Pierce, 1957) and intracranial structures (Sullivan, 1957) are made in this paper.

Material

This report is based on 100 cases admitted to the Hospital for Sick Children between September, 1951, and March, 1957. The diagnosis was confirmed by marrow examination in every case. Twenty other children attending with leukaemia during the same period are omitted because 17 of them were treated elsewhere after confirmation of the diagnosis and three were suffering from lymphosarcoma with leukaemic termination.

TABLE I.—*Age and Sex Distribution in 100 Cases of Leukaemia in Childhood*

Age on Admission (Years)	Males	Females	Total
0–1	1	3	4
1–2	3	4	7
2–4	15	10	25
4–6	10	12	22
6–8	11	12	23
8–10	7	6	13
Over 10*	4	2	6
Total	51	49	100

* Twelve years is maximum age for admission.

The age and sex distribution are shown in Table I. Sex incidence was equal. Aetiological factors were not investigated, as those children who died between 1953 and 1955 had already been included in a study on the antecedents of childhood leukaemia (Stewart *et al.*,

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1958); three of our series were mongols, an incidence similar to that of the above survey.

Clinical Features

A summary of the presenting symptoms and signs is shown in Table II. The average duration of history was six weeks. Eight children had had symptoms for less than one week; three had been ill for over one year. Pallor, limb pain, and skin haemorrhages were prominent initial symptoms. A few patients presented with swellings involving skin (four cases), bone (two cases), vulva (one case), and parotid glands (one case). In three cases proptosis was a presenting feature; hemiplegia was an initial manifestation in two, while facial and third-nerve palsy were presenting signs in one case each.

TABLE II.—*Initial Clinical Picture* (100 *Cases*)

Main Symptoms	No. of Cases	Main Signs	No. of Cases
Pallor	54	Pyrexia	80
Malaise	51	Lymphadenopathy	75
Limb pain	37	Splenomegaly	73
Anorexia	23	Hepatomegaly	69
Bruising	23	Petechiae or ecchymoses	65
Neck swellings	12	Ulceration of mouth or fauces	11
Vomiting	12	Skin infiltration	4
Cough	8	C.N.S. signs	4
Backache	5	Proptosis	3
Dyspnoea	5		

Initial Haematology in the Acute Cases (98 Patients)

Table III shows that leucocytosis (30 cases) was encountered more often than leucopenia (25). Leucocytosis was nearly always accompanied by abnormal cells in the peripheral blood (26 out of 30); in contrast, cases without leucocytosis frequently had only mature cells in the differential count (32 out of 68). Fourteen children had a haemoglobin level over 75% (11 g. per 100 ml.) when first seen, and in six of these leukaemic (blast) cells were not seen initially in the peripheral blood. Bone-marrow examination disclosed a normal picture on the first occasion in three children; in a further case the marrow was aplastic and in another hypoplastic. The marrow in all other cases was already leukaemic on initial examination. Precise subdivision of leukaemic cells into lymphoblastic and myeloblastic types was not attempted, because differentiation between these stem cells is not feasible by ordinary haematological techniques. Special categories recognizable in this series by their haematological findings and clinical course were acute monoblastic, acute plasma-cell, and chronic myeloid leukaemia.

TABLE III.—*Representative Peripheral Leucocyte Count in Untreated Stage* (98 *Cases of Acute Leukaemia*)

Total White Blood Cells	No. of Cases	Predominant Cell Type: Polymorphs (No. of Cases)	Predominant Cell Type: Lymphocytes (No. of Cases)	Predominant Cell Type: "Blast" Cells (No. of Cases)
Under 5,000 per c.mm. (leucopenia)	25 } 68	4*	51†	13
5,000–15,000 per c.mm.	43 }			
Over 15,000 per c.mm. (leucocytosis)	30	3‡	8§	19
Total	98	7	59	32

* 1 had leukaemic cells. † 18 had leukaemic cells. ‡ 3 had leukaemic cells. § 4 had leukaemic cells.

Acute Monoblastic Leukaemia (5 Cases)

Cells resembling primitive monocytes were found in blood and bone marrow. Ulceration of skin and oral mucous membrane was frequent. There was a rapid deterioration in all five. Remission was not obtained in the two cases treated.

Plasma-cell Leukaemia (1 Case)

S. M., a female aged 7 months, developed pallor, refused to feed, and vomited blood. Slight jaundice was present. Petechiae were found on the soft palate. There was marked enlargement of the liver and spleen. The haemoglobin level was 48% (7.1 g. per 100 ml.). Initial leucocyte count was 8,400 per c.mm., with 64% lymphocytes and 36% polymorphs. Primitive cells were also absent in the only subsequent blood count. The bone marrow contained numerous round reticular basophil cells, compatible with either erythroid or plasma-cell origin. Filter-paper electrophoresis of the patient's serum showed an abnormal pattern (α_1 globulin high, α_2 globulin low, β globulin possibly raised; no comment was made regarding the γ-globulin band). Progress of the disease was rapid and the infant died after two weeks in spite of blood transfusion and cortisone therapy.

At necropsy the liver, spleen, and kidneys were enlarged. The bone marrow showed a uniform gelatinous, reddish-pink appearance. Microscopically, there was a general infiltration by abnormal cells involving extensively the bone marrow, liver, and spleen, and foci of infiltration were present in the kidneys, lungs, and lymph nodes.

Cytology of Leukaemic Cells.—The infiltrate consisted of large cells which varied from 15 to 20 μ in diameter. They had disproportionately large, rounded nuclei which, in

TABLE IV.—*Details of* (*a*) *Five Cases of Monoblastic Leukaemia and* (*b*) *Two Cases of Chronic Myeloid Leukaemia*

Age	Sex	Length of History	Presenting Symptoms	Enlarged: Liver	Enlarged: Spleen	Enlarged: Lymph Nodes	Haemoglobin (g. per 100 ml.)	Initial Leucocyte Count (per c.mm.)	Differential Leucocyte Count	Bone-marrow Cell Count	Treatment	Survival After Diagnosis
(a) Five Cases of Monoblastic Leukaemia												
8 mths	F	2 mths	Upper respiratory infection	+	+++	+	6·5	5,800	63% monoblasts	100% monoblasts	Cortisone	4 mths
9 ,,	M	7 ,,	Skin lumps; sore throat	+	+	+	10	6,700	24% monoblasts	100% monoblasts	Nil	3 ,,
9 yrs	M	1 week	Bleeding	0	0	0	7·5	29,000	100% monoblasts	100% monoblasts	Transfusion	2 days
11 ,,	M	6 mths	Rash on arms and legs	+	0	0	7·0	5,300	65% monoblasts	100% monoblasts	,,	2½ mths
12 ,,	F	1 mth	Sore throat	+	++	Neck only	3·6	77,800	82% monoblasts	100% monoblasts	Cortisone, aminopterin, 6-mercaptopurine, nitrogen mustard	4 ,,
(b) Two Cases of Chronic Myeloid Leukaemia												
7 yrs	F	21 mths	Joint pains and fever	+	+++	+	7·7	256,000	76% polymorphs	22% premyelocytes	Deep x-ray therapy	3 yr 6 mth
8 ,,	F	4 ,,	,, ,,	0	+	0	12·1	133,000	99% polymorphs	35% premyelocytes	,, ,,	5 yr 3 mth

addition to moderate general basophilia, contained coarse clumps of chromatin of irregular arrangement, one to three or more large nucleoli, and a well-defined nuclear membrane. The cytoplasm was sometimes inconspicuous, sometimes pale and immolated, but was frequently homogenous and deeply staining, with a slight or moderate basophilia. The nuclei commonly occupied an eccentric position in the cytoplasmic mass, and sometimes there was a faint perinuclear halo of paler cytoplasm. Occasional cells possessed two or even more nuclei. There were some mitotic figures. In sections of spleen and bone marrow stained with methyl green and pyronine an appreciable portion of the neoplastic cells showed a definite coloration of thin cytoplasm. The appearance supported the evidence obtained from bone-marrow smears during life, that the neoplastic cells were primitive forms of plasma cells.

Chronic Myeloid Leukaemia

The two cases are summarized in Table IV. They were characterized by a long history, polymorphonuclear leucocytosis in the peripheral blood, and an excess of myelocytes in the marrow. Aged 8 and 12 years respectively, they were treated with *x* rays and transfusions and survived for three and five years.

Radiology of 50 Acute Cases

Complete or partial skeletal surveys on 50 patients showed radiological changes in 33 (66%). This incidence is likely to be higher than that of an unselected series, because radiographs were often requested on account of skeletal symptoms. The femora and tibiae were the most frequently involved (Table V); only once were

TABLE V.—*Skeletal Survey* (50 *Cases*)

Bone *X*-rayed	No. of Cases	Abnormal	
		No.	%
Femur	44	26	59
Tibia and fibula	42	24	57
Spine	26	8	31
Humerus	33	9	27
Radius and ulna	28	8	29
Skull	16	4	25
Hands	9	2	22
Pelvis	27	5	18
Ribs	27	2	7

they radiologically normal in the presence of bone changes elsewhere. The skull showed infiltration in four cases (Special Plate, Fig. 1). Radiological changes were present in the spine in eight cases (Special Plate, Fig. 2), and in two of these preceded evidence of leukaemia in the peripheral blood.

P.B., a female aged 3 years, had had lumbar pain for two months and a limp for two weeks; restricted movement in the lower spine was the only clinical sign. Radiographs showed anterior wedging of the fourth and fifth lumbar vertebrae. Initial blood count and marrow findings were within normal limits. Haematological evidence of leukaemia appeared three months later. The patient lived for eight months receiving remission therapy.

L.D., a female aged 8 years, presented with a three-months history of backache and abdominal pain. On admission there was unilateral proptosis with third-nerve palsy on the same side. Bone pain became a prominent feature. Radiologically there was progressive collapse of vertebral bodies, and extensive rarefaction involving several long bones, with the subsequent development of pathological fractures. The serum calcium rose to 14.6 mg. per 100 ml. The marrow contained primitive cells at an early stage, but leukaemic cells were not found in the peripheral blood until several months after radiological changes appeared. Her response to remission treatment was poor.

Table VI shows that metaphysial translucent bands of rarefaction were the commonest findings in the long

TABLE VI.—*Bone Changes* (33 *Cases*)

	No. of Cases	%
METAPHYSIAL TRANSLUCENT BAND	29	88
CORTICAL INVOLVEMENT	20	61
Round translucent areas	13	
Sclerosis	7	
Spontaneous fracture	6	
Generalized rarefaction	2	
PERIOSTEAL INVOLVEMENT	9	27
Irregularity	5	
Double contour	4	
Subperiosteal calcification	3	

bones (Special Plate, Fig. 3), occurring in 88% of all cases with *x*-ray changes. Cortical changes (61%) came next in order of frequency, often taking the form of translucent areas in the diaphysis; these areas were sometimes extensive and the cause of spontaneous fractures (Special Plate, Fig. 3); occasionally sclerosis was seen. Periosteal involvement (27%) consisted of irregularity, double contour, or subperiosteal calcification (Special Plate, Fig. 4). Epiphysial changes were not observed in this series, although we had previously seen epiphysial involvement of the femoral head resembling Perthes's disease in a 12-year-old boy with chronic myeloid leukaemia.

Treatment

The series included 30 patients ("untreated cases") who were seen mainly in the early part of the period under review and received, at most, blood transfusions or antibiotics. There were also 63 patients ("treated cases") who received one or more courses of steroids, aminopterin, or 6-mercaptopurine. It should be noted that amethopterin ("methotrexate") was not available in Great Britain during most of the review period. The remaining cases included two cases of chronic myeloid leukaemia and five cases of acute leukaemia treated with agents subsequently judged to be inoperative.

Table VII shows that half the "untreated" children had died within three months of their first symptoms, while it was seven months before the same proportion

TABLE VII.—*Results of Treatment: Survival from Onset of Symptoms*

	Supportive Treatment Only	Supportive and Anti-leukaemic Treatment
50% dead	3 months	7 months
75% ,,	6 ,,	11 ,,
100% ,,	1 year	2 years, 6 months

TABLE VIII.—*Relation of Chemotherapy to Survival*

Chemotherapy	No. of Cases	Average Survival in Months	
		From Onset	After Treatment
None	30	3·0	—
Cortisone	16	5·5	4·0
Cortisone and aminopterin	17	8·8	6·5
Cortisone and 6-mercaptopurine	9	10·8	8·6
Cortisone, aminopterin, and 6-mercaptopurine	15	13·3	10·7

had died among the "treated" group. All untreated children died within one year, at which time nearly a quarter of the treated group were still alive. The longest survival, 30 months, was observed in a boy aged 5 years with acute undifferentiated leukaemia; he had five remissions, the highest number in the series.

Table VIII shows the average survival time in months after the first symptom according to the drug(s) given during the whole course of the illness. The average survival time increased progressively from 5.5 months

when steroids were the only agents given, up to 13.3 months when all three antileukaemic agents were used.

General Pattern of Remissions

Serial examinations of the bone marrow were not performed as a routine, and we have used the term "complete remission" to imply (1) abeyance of all symptoms and signs; (2) a sustained satisfactory haemoglobin level (over 11 g. per 100 ml.); (3) the disappearance of abnormal cells from the blood and a return to normal of the total and differential leucocyte count. The term "partial remission" implies an amelioration in symptoms, signs, and blood picture short of the above criteria. In patients who received a transfusion as well as remission treatment, improvement sustained for at least six weeks was required because a short remission sometimes follows a transfusion.

Of the 63 treated patients, 34 (54%) had at least one complete remission, while a further 14 (22%) underwent partial remissions. Thus temporary improvement occurred in 76% of the treated cases. The number of cases remitting after a second, third, and fourth course was 16, 6, and 3, respectively. A second remission (partial or complete) occurred in 46% of patients who had complete initial remission and in only 15% of those who had had partial first remissions.

Steroid Remissions

Thirty-five children were treated solely with steroids as their first course of remission therapy. In this group there were 18 complete and 8 partial remissions, giving an improvement rate of 74%. Fourteen children received a second course of steroids, and five had a remission. Experience was mainly with cortisone, the dosage of which varied from 50 mg. daily for five days to 300 mg. daily for several weeks. The lowest dose which induced a complete remission was 100 mg. daily given for a week to a 7-year-old boy. Thirteen children received less than 200 mg. daily during the first week of cortisone therapy, and only four of these had a remission; in contrast, 22 courses of 200 mg. or over during the first week were followed by 14 remissions, a significantly better result ($P = <0.02$). A remission followed an increase in dosage to 300 mg. daily in two cases in which a dosage of 200 mg. had failed.

Continuous treatment with steroids from one active leukaemic phase through remission until the next relapse carried no apparent advantage over the administration of separate short courses in the few cases analysed (see Table IX). More data on this point are desirable. In two children given cortisone continuously for over three months vertebral collapse developed. This complication was not encountered as a direct result of short courses of cortisone, though one patient showed deterioration of pre-existing leukaemic vertebral damage.

TABLE IX.—*Comparison of Short Courses and Prolonged Course of Steroid Therapy*

First Steroid Therapy	No. of Cases	Remission in Months		
		Shortest	Longest	Average
Short courses (less than one month)	6	1	7	4·5
Long course (continued until next relapse)	9	1	7	4

Other side-effects were slight, even when cortisone was administered continuously for four weeks in a daily dosage of 200–300 mg. Four children developed hypertension and three others had pyodermia. Two children had temporary rises in blood urea level, reaching 430 mg. per 100 ml. in one. This effect was thought to be partly related to the rapid shrinkage in size of a heavily infiltrated liver and spleen.

Remissions induced by steroids were usually quicker and more distinctive than those following antimetabolite therapy. In febrile cases the earliest clinical sign of an impending remission was a prompt return of the temperature to normal. Remissions followed in 81% (26 out of 32) of children in whom pyrexia had resolved within three days of starting steroid therapy, but in only 23% (5 out of 22) of those still febrile on the third day. The subsequent clinical picture of remission was a return of well-being, fading of purpura, and diminution of hepatic, splenic, and lymph-node enlargement.

Haematological evidence of remission usually occurred 10–14 days after starting treatment, and often resulted in severe leucopenia in cases where the leucocyte count was already low. A fall in the haemoglobin level was another early change, and in one-third of cases was in excess of 4 g. per 100 ml. Failure to meet this situation by timely transfusion was probably the cause of death in one cortisone-treated patient whose haemoglobin level was low initially. Transfusion was given in the first ten days of therapy during 41 out of 86 remission courses in which steroids were concerned, alone or in combination. Second or subsequent transfusions were necessary in six children in whom the first transfusion had failed to prevent a fall in haemoglobin level of over 4 g. per 100 ml.

The clinical and haematological findings before steroid therapy were analysed to see if any reliable method existed of foretelling the chance of a remission. Table X shows that relatively unfavourable signs for

TABLE X.—*Influence of Initial Leucocyte Count and Predominant Cell on Remission with Steroid (First Course)*

Predominant Cell	Remissions			
	None	Partial	2–6 Months	Over 6 Months
Neutrophil	4	1	0	0
Lymphocyte	5	6	13	6
Blast cell	5	7	6	0

Total Count	None or Partial	Over 2 Months
Under 5,000 per c.mm. ..	6	8
5,000–15,000 ,, ,, ..	15	13
Over 15,000 ,, ,, ..	11	3

developing a remission were peripheral leucocytosis and neutrophil predominance in the differential count. Severe anaemia, a clinical history of under one week, and absence of generalized adenopathy in cases showing other systemic leukaemic effects were also indications that a steroid remission was unlikely. Relatively favourable signs were the absence of leucocytosis or a differential count which was predominantly lymphocytic. No guide was obtained from haemorrhagic manifestations or the degree of enlargement of liver or spleen.

6-Mercaptopurine Remissions

In 24 children the first course of 6-mercaptopurine was sufficiently free from overlap with other agents to judge the separate effect of this drug. Three complete and five partial remissions resulted, giving an over-all

remission rate in this small group of 33%. Only one child in five experienced remission after a second course. The usual dosage was 2.5 mg. per kg. per day and the range fell between 25 and 100 mg. daily. 6-Mercaptopurine was usually discontinued if the total leucocyte count fell below 1,000 per c.mm., and, using this precaution, no severe toxic effects were encountered even after prolonged therapy. In seven cases azaserine (diazoacetylserine) was combined with 6-mercaptopurine, but no synergic effect was manifest in these few cases, and therapy had to be discontinued in two owing to oral sepsis or gastro-intestinal bleeding.

In some cases a study of the leucocyte count during treatment gave the first information that a remission was impending. In two complete remissions the earliest sign was a diminution in circulating leucocytes about the third day, which became most marked at the eighth and tenth days respectively. In two partial remissions an initial drop appeared between the third and seventh days, reaching a lowest level on the nineteenth and twenty-eighth days, respectively.

Aminopterin Remissions

Fourteen children had a first course of aminopterin which was uninfluenced by overlap with the other agents. Two complete and three partial remissions resulted, giving a remission rate in this small group of 38%. Ten other children received a first course which consisted both of steroids and of aminopterin simultaneously, and six remissions resulted; this rate was no different from that when the first course consisted of steroids alone.

The usual dosage of aminopterin was 0.25–0.5 mg. daily, but it was possible sometimes to raise the dose cautiously to 1.0 mg. daily, and three of the aminopterin remissions were obtained in this way. Liability to oral ulceration after aminopterin therapy necessitated observation in hospital. Daily inspection of the buccal mucosa allowed early recognition of patchy desquamation and whitening inside the lips and on the palate. In such cases it was possible sometimes to forestall oral ulceration by withdrawal of the drug for a few days; lozenges containing folinic acid (citrovorum factor) were sometimes given for a presumed topical effect. Leucopenia, rash, and alopecia were additional complications.

In some cases the leucocyte count gave information about an impending remission before clinical improvement occurred; in the case of two complete remissions a diminution in circulating leucocytes took place within three days of starting treatment, with maximum effect on the seventh and fourteenth days respectively.

Meningeal Syndrome

With increased survival in cases of acute leukaemia, symptoms of meningeal involvement have become more frequent. Sullivan (1957) reported the development of a meningeal syndrome in a quarter of cases of acute leukaemia treated with cortisone or chemotherapy at the Anderson Hospital and Tumor Institute of Texas Medical Center. Radiographs of the skull often showed widening of the sutures, and the cerebrospinal-fluid pressure was sometimes increased, often with pleocytosis and increased protein. Systemic hypertension and obesity were also observed. It was concluded that antileukaemic drugs probably cross the blood–brain barrier in reduced concentration, and may fail to influence intracranial infiltration though the systemic lesions may be under more satisfactory control. Sullivan suggested that irradiation of the skull, or aminopterin given intrathecally, may relieve symptoms due to meningeal involvement. In our series of 100 cases several had neurological signs, but only one had the symptoms and signs of the meningeal syndrome.

C.F., a male aged 8 years, had pallor, lassitude, and limb pain. His acute leukaemia went into partial remission after administration of steroids and 6-mercaptopurine. Two months later he became deaf and developed proptosis. *X*-ray examination of the skull showed evidence of extensive leukaemic infiltration. He was given aminopterin, but soon developed headaches, vomiting, and neck stiffness. Papilloedema and retinal haemorrhages were present. The cerebrospinal fluid was not examined. A further course of steroids was given, but failed to control the meningeal phase of the disease; death occurred during a convulsion.

After our analysis had been completed, another example of the meningeal syndrome was received into the hospital for treatment.

P.F., aged 10, presented with pallor and purpura, found to be due to acute leukaemia. The first examination showed 360,000 leucocytes per c.mm. A remission followed treatment with steroids and 6-mercaptopurine. Two months later she developed headache, vomiting, and vertigo. On admission, papilloedema and retinal haemorrhages were present. A radiograph of the skull was normal. The cerebrospinal fluid contained 1,835 leucocytes per c.mm., of which the majority were leukaemic (blast) cells; protein 10 mg. and sugar 80 mg. per 100 ml. Deep *x*-ray therapy to the posterior fossa in a total dosage of 500 r over ten days resulted in improvement in the papilloedema and reduction in cerebrospinal-fluid pleocytosis to 95 per c.mm. The patient was discharged two weeks later in full remission and without meningeal signs.

Infiltration of Kidneys

Many treated cases showed enlarged kidneys at post-mortem examination. This renal enlargement usually went unrecorded in life, but was a striking finding at necropsy. This impression was confirmed when the weights of the kidneys of treated and untreated cases were compared, normal values being taken from the hospital necropsy records and allowance being made for age. Kidneys of more than double the expected weights were found in 18 out of 24 treated cases (75%) as opposed to 5 out of 19 untreated cases (26%). The possibility of such a finding occurring by chance is remote ($P = <0.02$). The degree of renal enlargement did not appear to vary with the antileukaemic agent used or with the degree of associated enlargement of liver or spleen. Microscopically, the enlargement was found to be due to extensive leukaemic infiltration. This infiltration, which was never severe enough to produce uraemia, was presumably related in some way to the effects of treatment. It cannot be explained on the grounds of increased survival time, as treated patients with enlarged kidneys usually succumbed quite early—an observation also made by Pierce (1957).

Discussion

Remission treatment has become almost a standard practice for acute leukaemia, because it offers a high expectation of clinical improvement and the risks of toxicity with modern methods are small. Since remissions alone, and never cures, have been obtainable by use of the present antileukaemic drugs, a more fundamental form of treatment is needed urgently. One possibility follows upon the animal work of

Medawar (1958) on homografts with tissue cells, following which grafts of foetal haemopoietic tissue after total body *x*-irradiation have been tried (Thomas *et al.*, 1959). The hope of ultimate success from this or other methods gives a further measure of justification for the interim use of the agents capable of inducing remissions.

In the present series clinical improvement occurred in 76% of the cases, usually without discomfort to the patient, and the duration of stay in hospital was kept to a minimum. Some of the children were able to return temporarily to school. The true prognosis of leukaemia was always given to the parents, and treatment was carried out only after full explanation and if it was desired.

The question arises as to the place which is most appropriate for supervision of patients under treatment for acute leukaemia. Using a pre-planned regimen, Farber (1958) was able to report that 10% of a consecutive series of 900 leukaemic children were still surviving two and a half years after the onset of the disease. Such a result suggests that, in spite of the distance and discomfort sometimes involved, there is some advantage to be gained by over-all supervision in a special centre. When the appropriate therapy has been instituted and a remission obtained the patient can return home until a relapse occurs, follow-up blood counts being arranged at the nearest convenient laboratory.

Now that a choice of antileukaemic agents is available, their order of administration has to be decided. In the present series the three drugs used were usually given in sequence, because we found no evidence of synergic effect, nor was resistance to individual components prevented by combinations of drugs.

Steroids were found to be the most effective and rapidly acting drugs, particularly for the acute stages with thrombocytopenia and anaemia. In other cases they were usually held in reserve for the time when both aminopterin and 6-mercaptopurine had failed. This series gave information with respect to treatment with cortisone rather than the newer analogues. A dosage of cortisone smaller than 200 mg. daily for two weeks failed to give a good remission rate. For rapid action steroids were given intravenously in the form of hydrocortisone or corticotrophin. After a patient had become apparently resistant to cortisone, a further remission was sometimes obtained by an increase in dosage to 300–400 mg. daily or by a change in preparation to one of the newer analogues or to corticotrophin. Experience in the present cases suggested that it is reasonable to combine an antimetabolite with cortisone in certain cases in the acute stage—namely, when there is leucocytosis, polymorphonuclear predominance in the peripheral count, or a very short clinical history. The results also suggested that administration of antimetabolites should be started in acute cases treated with steroids when the initial fever fails to resolve within three days of beginning therapy. Otherwise it was unusual for aminopterin or 6-mercaptopurine to give a successful remission in cases which had failed to respond initially to steroids, but the adjuvant value of including them in the regimen raised the survival time considerably over that of cases treated with steroids alone.

When a remission is obtained the question arises whether to continue on a maintenance dose of the drug. Our relatively small data showed no advantage from maintenance steroid therapy, while vertebral collapse occurred in two cases. It was our definite impression that maintenance treatment with 6-mercaptopurine was useful in prolonging remissions, but overlap with other agents made quantitative assessment impossible.

Summary

Observations are presented on 100 consecutive patients seen at the Hospital for Sick Children, Great Ormond Street, with leukaemia (acute undifferentiated, 92; acute monoblastic, 5; chronic myeloid, 2; and plasma-cell, 1).

On admission the commonest symptoms were pallor, limb pain, and bruising, and the commonest signs were fever, lymphadenopathy, and hepatosplenomegaly. The total white-cell count was normal in nearly one-half; 25% had leucopenia and 30% leucocytosis. Abnormal white cells were present at the initial peripheral blood count in 58%. Radiological bone changes occurred in two-thirds of those *x*-rayed; the tibia and femur were the most frequent sites of involvement, and were rarely normal when bone changes were present elsewhere.

Of 63 patients receiving one or more courses of steroid, aminopterin, or 6-mercaptopurine, 34 (54%) had one or more complete clinical remissions of up to seven months in duration. A further 14 (22%) had partial remissions, giving improvement in a total of 76%. In those treated with all three drugs (later in the series) the average survival time was 13.3 months, as opposed to three months in untreated cases. The longest survival in the series was 2½ years.

Steroids proved the most frequently effective of the remedies used: the earliest sign of remission was a prompt return of the temperature to normal; further leucopenia and a fall in haemoglobin level were frequently seen at the onset of remissions; leucocytosis and neutrophil predominance were relatively unfavourable to the development of a steroid remission.

Present-day therapy not only prolongs the course of leukaemia, but also influences the manifestations. Mention is made of meningeal and renal involvement.

We gratefully acknowledge the help of many colleagues, including the following: the physicians of the hospital who had care of these patients; the staff of the Department of Clinical Pathology, initially under Dr. I. A. B. Cathie, and subsequently under Dr. R. M. Hardisty, to both of whom we are also grateful for valuable comments; the staff of the Department of Morbid Anatomy, under Dr. Martin Bodian; Drs. L. G. Blair, and J. Sutcliffe, who are responsible for all the radiology; the Department of Medical Illustration, under Mr. Derek Martin; the nursing staff; and the staff of the Records Department. We are also indebted to Professor Alan Moncrieff, Dr. J. D. N. Nabarro, and Dr. R. E. Bonham Carter for constructive criticism.

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CARCINOMA OF THE STOMACH

AN EVALUATION OF DIAGNOSTIC METHODS INCLUDING EXFOLIATIVE CYTOLOGY

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[WITH SPECIAL PLATE]

Carcinoma of the stomach is often not diagnosed until the growth has reached an inoperable stage. In recent years there has been renewed interest in the study of exfoliated cells from gastric tumours in an attempt to make the diagnosis earlier than is possible by conventional methods (Papanicolaou, 1946; Swarts *et al.*, 1950; Lemon, 1952; Rubin *et al.*, 1953). In Great Britain Schade (1958) has diagnosed carcinoma of the stomach on 25 occasions when both barium-meal and gastroscopic findings were still negative. Stimulated by this work, we have evaluated the various diagnostic methods suitable for out-patient study, and in this report we present the results, referring particularly to the use of exfoliative cytology as a supplement to radiology and gastroscopy.

Design of the Investigation

All patients seen in the out-patient clinics of two surgical units over a period of nine months were included in the series if there was clinical suspicion of carcinoma of the stomach. The series includes a number of patients known to have a gastric ulcer but whose recent symptoms suggested the possible development of carcinoma. A barium-meal examination was first carried out, and so far as was possible all radiology in the series was performed by one person, who was aware only of the provisional clinical diagnosis. If the barium studies revealed no contraindication gastroscopy was then carried out, again so far as possible by one person who did not have access to the case record or the barium-meal report at the time of gastroscopy. Material for cytological examination was obtained immediately before gastroscopy. The patient fasted for at least 10 hours before the examination (if any evidence of pyloric obstruction was present the stomach was washed out through a wide-bore tube on the evening before the test). The method used was essentially similar to that described by Schade (1958). No mucolytic or abrasive methods were used to obtain cytological specimens. A No. 14 Levine tube was introduced through the mouth into the stomach, and 100 ml. of normal saline solution was injected by means of a rubber urethral syringe (2 oz; 57 ml.). The stomach was then evacuated as completely as possible, using a suction apparatus. In a very few cases, to facilitate insertion of the tube, the patient drank a glass of tap-water; the injection of the 100 ml. of saline was omitted in these cases, and the water and stomach contents were evacuated. Either of these aspirates constituted the first specimen. A further 100 ml. of saline was injected into the stomach, and partially withdrawn and forcibly reinjected several times. The tube was then clamped, the patient instructed to lie in turn in the prone, supine, and lateral positions, to sit up, and finally to walk if ambulatory. The stomach was then aspirated to obtain the second specimen. Both specimens were lightly centrifuged immediately, the sediment smeared on glass slides, and then stained by Papanicolaou's method. The cytologist did not have access to the radiological or gastroscopic findings.

The surgeon responsible for each patient decided for or against operation by reviewing the clinical, radiological, and gastroscopic evidence. The cytopathological report was consulted only on occasions when a decision was made against operation because of negative radiological and gastroscopic reports or when an apparently normal stomach was found at operation. If gastrectomy was performed, the resected specimen was immediately fixed for subsequent histological studies.

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Results

Sixty-eight patients were thought to have a possible gastric carcinoma when first seen. This diagnosis was finally confirmed histologically in 24 (35.3%). The age and sex distribution are shown in Table I. Radical resection was carried out in 12 of the 24 patients with carcinoma; in at least two of these the lesion was probably beyond the scope of surgery though it was resectable. A palliative resection was done in 5, and no treatment was possible in 7.

Of the remaining 44 patients, 38 (55.9% of the total series) were found to have non-malignant conditions, and in 6 (8.8%), whose gastric symptoms were of brief

TABLE I.—*Age and Sex Distribution in 68 Cases in Which Carcinoma of Stomach was Suspected on Clinical Grounds*

Age Group (Years)	No. of Patients	Patients with Carcinoma		
		Male	Female	Total
30–39	5	1	0	1
40–49	10	1	0	1
50–59	22	5	2	7
60–69	20	7	5	12
70–79	10	0	3	3
80–89	1	0	0	0
Total	68	14	10	24

TABLE II.—*Final Diagnosis in 68 Patients Suspected Originally to Have Gastric Carcinoma*

	No. of Patients
Carcinoma of stomach	24
Gastric ulcer	16
Duodenal ,,	10
Gastric ulcer and duodenal ulcer	1
Atrophic gastritis	5
Functional pyloric obstruction	1
Psychogenic gastric upset	1
Gastric erosions	1
Hiatus hernia	1
Hodgkin's disease	1
Diverticulitis	1
No firm diagnosis established	6
Total	68

TABLE III.—*Carcinoma of Stomach: Comparison of Results of Three Diagnostic Methods*

	Radiology	Gastroscopy	Cytology
A. Entire series (68):			
Total investigated	68	64	68
,, failures	0	8	5
False-positive carcinoma	0	2	1
B. Histologically confirmed carcinoma (24):			
Total investigated	24	22	24
Carcinoma diagnosed	23 (96%)	17 (78%)	13 (54%)
Technical difficulties	0	3	2
False-negative carcinoma	1 (4%)	2 (9%)	9 (38%)

duration and abated spontaneously, no firm diagnosis was reached (Table II). The results obtained from radiology, gastroscopy, and cytology are compared in Table III.

Radiology

Barium-meal examination was carried out in all 68 patients. It was definite or suggestive of carcinoma in 23 (96%) of the 24 patients who were found to have a histologically confirmed carcinoma. The one false-negative result is discussed below (Case 34). In most cases the reports were unequivocal—for example, "constant filling defect, suggestive of carcinoma"; "high ulcer in the subfundic area, gastric carcinoma." In the non-malignant group no definite opinion which was shown to be a false positive was given. However, the radiologist expressed doubt as to the appearances on five occasions. A summary of these patients is given in Table IV.

TABLE IV.—*Carcinoma of Stomach: Findings in Five Patients With Suspicious Radiological Appearances*

Case No.	Radiology	Gastroscopy	Cytology	Final Diagnosis
11	Slight deformity lesser curvature, also duodenal ulcer	Normal	No malignant cells seen	Duodenal ulcer
15	Narrowing of antrum: ? disuse after gastrojejunostomy or ? carcinoma	Severe atrophic gastritis	,, ,,	Atrophic gastritis
21	Irregularity + induration of lesser curvature	Normal	(1) Pre-operative: highly suggestive of carcinoma; (2) Post-operation: normal	Nil found at laparotomy
32	Possibility of carcinoma raised in patient with hiatus hernia	,,	No malignant cells seen	Hiatus hernia
64	Hour-glass constriction at mid-gastric level	Failed; gastroscope arrested at cardia	,, ,,	Healing gastric ulcer

A malignant lesion was excluded by gastroscopy in four of the five cases. Gastroscopy failed in Case 64, a woman aged 69 who did not wish to be operated on, but a healing gastric ulcer was subsequently demonstrated radiologically. Cytological reports were similarly negative for carcinoma in four of the five cases in the group. In Case 21 (discussed below) the report, which suggested carcinoma, was shown to be misleading.

Gastroscopy

This was attempted in 64 of the 68 patients. It was not done in the remaining four either because of the refusal of the patient or because of the presence of an organic impediment to the passage of the tube—for example, an oesophageal diverticulum. Gastroscopy was carried out in 22 of 24 patients who were proved to have gastric carcinoma; a suspicious lesion or a definite carcinoma was seen in 17 (78%); the examination was incomplete or failed in three cases, but failure was suspected as being due to the presence of a large carcinoma, and this was later confirmed. Two false-negative results were obtained. In one, a patient shown at laparotomy to have an inoperable pyloric carcinoma, evidence of pyloric stenosis was found but no carcinoma. The other case in which a carcinoma was not seen is discussed below (Case 34).

In the remainder of the series (those with no proved gastric carcinoma) gastroscopy produced two false-positive results.

Case 13.—A lesion thought to be a carcinoma was seen at gastroscopy in a patient in whom barium-meal findings and cytology were normal. No carcinoma was found at operation, when the lesion was seen to be a duodenal ulcer; a repeat gastroscopy five months later was negative.

Case 26.—A large ulcer proximal to the angularis was thought to be malignant. Barium-meal examination showed a benign ulcer, and cytology was negative for malignant cells. At operation it proved difficult to decide whether the ulcer was benign or malignant, but histological examination after gastrectomy proved the ulcer to be benign.

In neither case did gastroscopy alter the treatment, as laparotomy was required in Case 13 on clinical grounds and gastrectomy was necessary in Case 26.

Exfoliative Cytology

This was attempted in all 68 patients in the series. It was unsuccessful in five owing to failure to obtain the specimen, insufficient material, or lack of co-operation by the patient. Cells described as suspicious or definitely malignant were found in 13 (54.2%) out of 24 patients who had a proved carcinoma. In one of them (Case 34) barium-meal examination and gastroscopy had been negative; comparison and correlation of the histological preparations and smears of the gastric washings proved interesting and instructive in the positive cases (Special Plate, Figs. 1–4). In two cases (8.5%) the material was found to be unsuitable for diagnosis; nine (37.5%) false negatives were obtained. Barium-meal findings were positive or highly suggestive in all nine, and gastroscopy was positive in six and suspected in two of the eight cases in which it was carried out. In all nine cases the lesion was a huge carcinoma which was fungating or ulcerating; three of the nine were inoperable, and in three others total gastrectomy was required with removal of other near-by structures—pancreas, colon, etc. Histological examination of the tumour when exfoliative cytology was negative showed an anaplastic carcinoma in four cases and poorly differentiated adenocarcinoma in four.

Only one apparently false-positive result (Case 21) was obtained, in a patient who has not so far been shown to have a carcinoma. In a reappraisal of the slides in this case it is clear that the report which indicated the presence of "cells highly suspicious of malignancy" was too strongly worded. The explanation of this mistake probably lies in the fact that this case occurred early in the series when the cytologist had insufficient experience of the appearances with the new technique.

Illustrative Cases

Case 34

This patient, a woman aged 59, had complained of vague indigestion for a number of years; in the two months before being seen she had anorexia and generalized weakness. Barium-meal examination was negative; gastroscopy showed general atrophy of the mucosa and diminished movement in the pyloric antrum, but no evidence of carcinoma. Cytopathology showed a single clump of malignant cells (Special Plate, Fig. 5). At laparotomy, which included gastrotomy, no carcinoma was found, but a high partial gastrectomy was carried out because of the cytological report. Examination of the resected specimen showed general mucosal atrophy. There were two small (6 mm. diameter) dome-shaped swellings in the mucosa of the anterior wall just below the lesser curvature 1 and 2 cm. from the pylorus respectively. Microscopical examination confirmed the presence of atrophic gastritis. The small papillary lesion (Special Plate, Fig. 6) showed acinar dedifferentiation and

increased mitotic activity (Special Plate, Fig. 7), and was considered to be a very early carcinoma.

The long clinical history was probably due to atrophic gastritis with a recent exacerbation. The minute carcinoma could scarcely have been responsible for any clinical symptoms, but would have been missed in an early operable state but for the use of cytopathology. The patient has remained well for 15 months since the operation. She has a good appetite, and her pre-operative gastric symptoms have not recurred.

Case 21

This patient, a woman aged 30, had a three-months history of anorexia, nausea, and abdominal discomfort. She had lost a stone (6.4 kg.) in weight in nine months. Barium-meal examination showed irregularity of the lesser curvature a little below the cardia; the contour was constant and seemed indurated. At gastroscopy the stomach appeared normal. Cytological examination showed cells highly suggestive of malignancy. At laparotomy no carcinoma or other abnormality was found; at gastrotomy the gastric mucosa was of the thickened, rugose variety but otherwise normal. A biopsy of glands from the lesser and greater curvatures revealed only catarrhal changes. The operator did not feel justified in proceeding to gastrectomy. A repeat cytological examination was carried out in the convalescent period, and on this occasion no malignant cells were seen. Radiological examination five months later showed giant-type folds in the upper part of the body of the stomach, but no other abnormality was demonstrated. This patient has now been followed up for nine months, and carcinoma has not developed.

Comment

The results given above again demonstrate that one patient in every two reaches hospital after the gastric carcinoma is inoperable. It is also clear that diagnosis is often all too easy on clinical grounds at the time of the first visit to the surgical out-patient clinic. However, we have been impressed with the value of the conventional aids to diagnosis. Barium-meal examination disclosed all the malignant lesions found in the series except one very small carcinoma (Case 34). Gastroscopy proved a valuable adjunct to radiology, particularly in the study of gastric ulcer and the demonstration of gastritis and erosions, and in those cases where radiology had raised some doubt whether the stomach was clear of carcinoma. In all cases except one (Case 34) these two examinations proved to be an efficient diagnostic screen.

At first glance the results of exfoliative cytology are disappointing. Carcinoma was diagnosed in only 54%, but the nine false-negative cases (38%) all occurred in patients with a large ulcerating tumour—where the diagnosis was already clear by the other methods. False-negative results in this type of case have been described by Lemon (1952) and Schade (1958), and may well be due to a layer of necrotic cells on the surface of the tumour (Umiker *et al.*, 1958).

A false-negative rate of 50% seems to be not uncommon (Swarts *et al.*, 1950; Lemon, 1952). Indeed, Papanicolaou and his co-workers believe that, if ideal multiple specimens are obtained and properly handled, accuracy of 60% is about the limit (Seybolt *et al.*, 1951). In an effort to raise this percentage, various mucolytic and abrasive substances have been used to improve the material obtained from gastric washings (Panico *et al.*, 1950; Rosenthal and Traut, 1951; Ayre and Oren, 1953; Van der Reis *et al.*, 1956; Cooper and Papanicolaou, 1953; Crozier *et al.*, 1956). However, there is no general agreement that the use of these methods has substantially increased the accuracy possible.

In our series this method was at a disadvantage in that, though the cytologist had had considerable experience with specimens of sputum and from the respiratory tract, he had not previously dealt with gastric washings. Nevertheless, one very early carcinoma has been demonstrated when other methods could not have succeeded. This compares with Schade's (1958) demonstration of one such case per 100 examinations, and we agree with him that exfoliative cytology is a potentially valuable diagnostic procedure in the investigation of such an important disease as carcinoma of the stomach, where early diagnosis even in a small percentage of cases is an advance.

We suggest that the results of our investigation indicate that exfoliative cytology is a valuable supplement to radiology and gastroscopy, and logically should be used in clinically suspicious cases when these latter methods prove negative. It is certainly not a good screening procedure. We further suggest that the method should be available as a part of a cytology service in the larger centres, since we believe that it has clinical value and is not economically wasteful, provided that its use is confined to judiciously selected cases, and, in particular, that the temptation to use it as a routine screening procedure is resisted.

Summary

A method suited to the evaluation of radiology, gastroscopy, and exfoliative cytology in the diagnosis of carcinoma of the stomach is described. Our results show that the combined use of radiology and gastroscopy provides a reliable diagnostic screening method.

In a series of 68 patients, exfoliative cytology revealed one early case of carcinoma of the stomach which the other methods could not have been expected to detect. Cytology is therefore a valuable adjunct when the routine methods give negative results in clinically suspicious cases.

The high incidence of false-negative results (38%) shows exfoliative cytology to be an unreliable screening test for carcinoma of the stomach.

Our thanks are due to our clinical colleagues, Professor C. F. W. Illingworth, Mr. D. H. Clark, and Mr. A. P. M. Forrest, for their willing co-operation and for allowing us to include their cases in the series. P. S. M. is grateful to Mr. Carrick Henderson for his technical help in the cytological investigation, and to Mr. George Kerr for the photographs.

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SOME AUSCULTATORY AND PHONOCARDIOGRAPHIC FINDINGS OBSERVED IN EARLY INFANCY

BY

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[WITH SPECIAL PLATE]

With recent advances in cardiac surgery, early recognition and accurate diagnosis of congenital heart disease is increasingly important. In early infancy, tachycardia, rapid respirations, and crying make auscultation no easy matter. Distinction of the abnormal from the normal is difficult, and evaluation of adjustments between intra- and extra-uterine life provides an additional problem. Auscultation is easier in children and the normal more clearly defined, but the assessment of systolic murmurs remains difficult.

The present study was designed to evaluate the normal cardiac status in infancy, and particularly the incidence and character of murmurs. A series of infants have been examined clinically under optimal conditions both before and after birth. Phonocardiograms were recorded from these infants and from others with known congenital heart disease.

Clinical Material and Methods

Mothers without rubella or unexplained illness during pregnancy and their infants born at the Canadian Red Cross Memorial Hospital, Taplow, were studied. Premature infants, those with any obvious congenital abnormality, and those developing an infection were excluded. The infants with known or suspected congenital heart disease were referred from the paediatric department of the same hospital or from the Royal Berkshire Hospital.

Auscultation

In all, 230 infants were studied each night of their hospital stay after the late evening feed, when they were sleeping, supine, and the nursery was quiet. Observations were made on heart rate, sounds, and the presence and character of murmurs. If an infant would not sleep the heart rate for that night was omitted. Of these infants, 55 were re-examined between the ages of 6 weeks and 6 months.

Phonocardiograms

Phonocardiograms were obtained from 59 of the main series between the ages of 6 hours and 8 days. Repeat tracings were obtained from 14 of those seen for follow-up between 4 and 6 months of age. Because of the non-portable nature of the machine, recordings could not be taken at birth or from sick infants. The machine used has already been described (Besterman and Harrison, 1953). Tracings were made either soon after or during a feed, and crystal microphones were applied by skin suction. With the use of small microphones, simultaneous records from base and apex could be obtained, together with lead 2 electrocardiogram. Often, however, better results were obtained by using a single larger microphone attached to the flattest portion of the upper left chest or apex. Recordings were made by suppressing frequencies below 75, 150, 300, and 600 cycles per second by selection of the desired filter within the amplifier.

The foetal phonocardiograms most suitable for this study comprised some 64 from non-obese patients within approximately six weeks of term, 27 of whom had repeat post-natal recordings. A microphone was placed on the abdominal wall where the foetal heart was maximal and the uterine souffle minimal; maternal phonocardiogram and lead 2 electrocardiogram were recorded simultaneously.

Results

Heart Rate and Rhythm

Recurrent irregularities in rhythm were noted in six of the 200 infants studied, and persisted for a maximum of seven days; sinus arrhythmia was not clearly demonstrated. For a very short period after birth the usual infantile rapid changes in rate response to crying and external stimuli were less marked. The mean sleeping heart rates in relation to age are given in Table I and plotted in Graph 1. These results show that there was a rise from the second to the eighth day, with the maximum increase between the fourth and eighth days. After this day the number of infants observed fell sharply, but the mean rate continued to increase until

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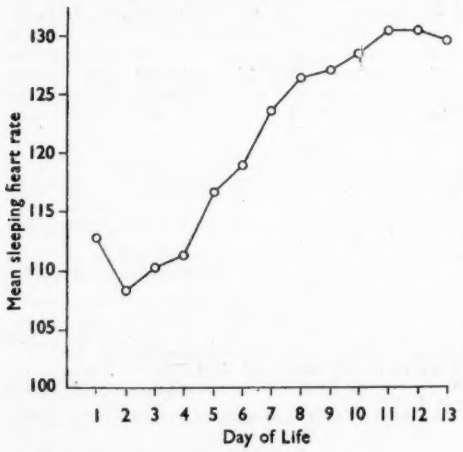
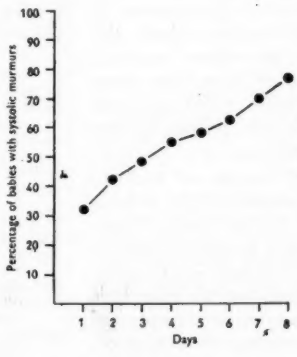
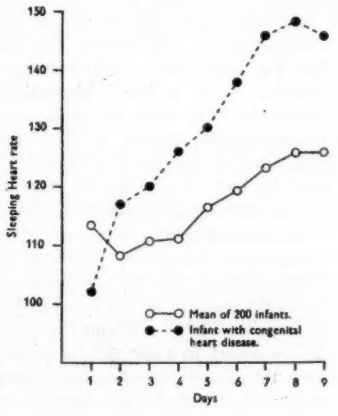


GRAPH 1



GRAPH 2



GRAPH 3

GRAPH 1.—Mean sleeping heart rate during first 13 days of life. GRAPH 2.—Percentage incidence of audible systolic murmurs in first 8 days of life. GRAPH 3.—Sleeping heart rate of infant who died with congenital heart disease compared with mean rate of 200 infants.

TABLE I.—*Mean Sleeping Heart Rate During First 13 Days of Life*

Day:	1	2	3	4	5	6	7	8	9	10	11	12	13
Mean sleeping heart rate ..	112·8	108·5	110·4	111·5	116·9	119·2	123·4	126·7	126·8	128·5	130·3	130·3	129·5
Number of babies	198	187	187	195	187	187	190	180	141	71	27	17	10

* The standard error of these means did not exceed a value of 0·8 beat per minute.

the eleventh day, after which there was a tendency to levelling off around 130 beats per minute. On the second day the minimum recorded rate was 76 and on the eleventh day 120 beats per minute.

A few of these infants were observed during and immediately after birth. The majority showed an immediate slowing followed by a sudden tachycardia after the first cry and a slow fall over the next 24 hours. The bradycardia appeared to bear a relationship to the degree of asphyxia, and a rate of 28 beats per minute was recorded in one asphyxiated infant. In some infants, however, the rate changed little immediately after birth, but fell slowly over the next 24 hours.

Heart Sounds

Both heart sounds were clearly heard all over the praecordium, in the epigastrium, and posteriorly; they were generally maximal towards the lower left sternal edge or between there and the apex. Splitting of first and second sounds was clearly audible from the time of birth, and for the first day or two there was commonly some accentuation of the pulmonary component of the second sound. Neither third nor auricular sounds were heard in any infant.

Phonocardiograms of the newborn infants clearly showed the components of the first and second sounds. The average time interval between the two major components of the second sound was 0.024 second. The minimum recorded was 0.01 second and the maximum 0.05 second, with individual variations up to 0.02 second. There was no obvious correlation between this split and the respiratory phase. The pulmonary component of the second sound was often well shown at the apex as well as at the pulmonary area (Special Plate, Fig. 2*b*) in contrast to its appearance in later childhood (Special Plate, Fig. 5).

The foetal tracings showed well-marked low-frequency ejection sounds, and most of the neonatal tracings also showed these sounds. In one infant a mid-systolic click was heard.

Irregular diastolic disturbances were shown in many of the low-frequency-range foetal recordings (Special Plate, Fig. 1*a*). The majority of neonatal phonocardiograms showed somewhat less well amplified disturbances with a constantly occurring deflection in each cycle (Special Plate, Fig. 3*b*). The average timing was 0.095 second after the first major component of the second sound; the individual minimum was 0.07 second and the maximum 0.12 second. These deflections were more impressive in some of the follow-up tracings, and possibly represent the third sound often audible in normal children, and registering as a sharper, somewhat higher-frequency sound (Special Plate, Fig. 5).

Variable low-frequency disturbances preceded the first heart sound in many tracings and were thought to represent auricular sounds.

Murmurs

All murmurs heard were systolic in timing, and their incidence in relation to age is shown in Table II and Graph 2. It will be seen that the incidence rose with each day of life. By the eighth day the incidence was

TABLE II.—*Percentage Incidence of Audible Systolic Murmurs During First 8 Days of Life*

Day:	1	2	3	4	5	6	7	8
Incidence % of systolic murmurs	33·5	43·0	48·3	55·6	58·3	63·5	70·4	77·4
Number of babies	230	230	230	230	230	230	230	230

77.4%. Systolic murmurs were heard in 48 of the 55 infants followed up. Phonocardiograms taken on an approximate quarter of the series confirmed this incidence.

In a small number of infants transient murmurs were heard soon after birth and persisting for minutes, hours, or a few days; they were noticed more frequently in infants anoxic at birth and in two babies with a severe respiratory infection. They were mostly long and high-pitched in character and localized around the pulmonary area. In one infant the murmur was thought to be continuous into diastole. No phonocardiograms of such murmurs were obtained.

Certain characteristics of the majority of murmurs may be defined. They were all short, of low or medium pitch, and mostly very soft or soft—Grade 1 or 2 of Levine's (1933) classification, and best heard with a bell stethoscope using light skin pressure. They were loudest in the first few quiet cycles following crying or other exercise, and became diminished or disappeared during deep inspiration or forced breath-holding, as did the heart sounds (modified Valsalva manœuvre). The majority were maximal at the lower left sternal edge or at some point between there and the apex, with varying propagation within this area; it was not unusual to hear these murmurs posteriorly or up in the neck. Others were maximal at the pulmonary area, with varying propagation towards the apex. Six infants had easily audible murmurs of a low-pitched, rasping character, maximal internal to the apex and widely propagated over the left praecordium. At follow-up the characteristics of these murmurs appeared to be identical with that found during the first week, though the six referred to above were all softer and less widely propagated. Phonocardiograms showed the murmurs to have a slightly delayed onset and to finish well before the second sound, the peak being in early or mid-systole. Characteristic murmurs are shown in Special Plate, Figs. 1, 3*b*, and 4, 7, and 8*a*. One of the six loud rasping murmurs is shown in Special Plate, Fig. 3*b*, but is not obviously distinguishable from the more common type of low-frequency murmur (Special Plate, Fig. 2*b*). Follow-up phonocardiograms in the same infants are shown in Special Plate, Figs. 3*c*, 4*b*, and 7*b*, and confirm the clinical impression of the unchanged character of the murmurs.

Comparison of Antenatal and Postnatal Murmurs

Systolic murmurs were shown in most of the better antenatal tracings. Characteristic murmurs are shown in Special Plate, Figs. 1*a*, 2*a*, and 3*a*, with postnatal tracings from the same infants in Figs. 1*b*, 2*b*, and 3*b*, respectively. The majority of prenatal murmurs had a late systolic component not seen in postnatal life, but such a murmur as that shown in Special Plate, Fig. 1*a*

appears to be similar to that shown after birth (Special Plate, Fig. 1*b*).

Two infants had murmurs picked up by the midwifery department with foetal stethoscope, thus raising the question of congenital heart disease. The characteristics of both murmurs were identical (Special Plate, Fig. 2*a*). In the first a low-pitched mid-systolic murmur became audible immediately after birth (Special Plate, Fig. 2*b*); the second had no murmur within minutes of birth and none at follow-up (Special Plate, Fig. 6). Both these infants had normal electrocardiograms and radiographs. Often no murmurs were audible at the time of birth, but sometimes either transient or definitive murmurs were noted at that time. However, listening conditions were not good.

Congenital Heart Disease

Satisfactory phonocardiograms were eventually obtained in most of the infants referred with known or suspected congenital heart disease. In many cases information on heart sounds and murmurs additional to that determined on clinical auscultation was obtained. Comparison with the normal series of phonocardiograms might show abnormalities in the second sound, such as abnormally wide splitting or accentuation, reduction, or absence of the pulmonary component. Abnormally intense third heart sounds, high-frequency ejection sounds (Special Plate, Fig 12), diastolic murmurs, and the varying character of the systolic murmurs could also be demonstrated. In most cases the character of the systolic murmurs was different from any demonstrated in the normal series. A few, however, demonstrated a murmur not dissimilar to those seen in the normal series, and in the absence of any obvious abnormality of the heart sounds auscultation and phonocardiography were of no diagnostic aid in such infants.

Special Plate Figs. 9*a* and 9*b* show the phonocardiogram of a 10-day-old infant who had subsequent post-mortem findings of infantile coarctation of the aorta, ventricular septal defect, and patent ductus arteriosus. He was in cardiac failure at 6 days and was diagnosed as having coarctation of the aorta on account of absent femoral pulsations and raised blood-pressure in the arms; at that time no abnormal auscultatory signs were detected. Phonocardiograms show an early systolic murmur in the anterior tracing and a late systolic murmur in the intrascapular area; there is some accentuation of the pulmonary component of the second sound and a diastolic murmur following the third sound, internal to the apex.

Special Plate Fig 10 is the phonocardiogram of a 5-weeks-old infant who was found to have a medium-sized ductus arteriosus at the time of operation at 7 months. She was breathless on feeding at 3 days, and clinical findings and ancillary investigations suggested the diagnosis of patent ductus arteriosus. At that time the auscultatory findings were of a loud, long, high-pitched systolic murmur at the pulmonary area. The phonocardiogram shows an intense high-frequency murmur at this area, spilling over a somewhat accentuated second sound; there is also a short diminuendo diastolic element.

The third illustration is that of the infant studied daily in the main series, who died at 6 weeks. Nothing abnormal was noted during early postnatal life. He subsequently became blue on feeding and was readmitted deeply cyanosed. Necropsy showed complete mitral atresia with interatrial communication, patent ductus arteriosus, and pulmonary artery and anteriorly placed aorta arising from the single functioning ventricle. Retrospectively, this infant had an unusually long murmur and a sleeping heart rate well above the mean for the series (see Graph 3). On the sixth to eighth day he had the highest recorded individual rate. Phonocardiogram at 3 days (Special Plate, Fig. 11*a*) shows the unusually long systolic murmur, which had changed by 5 weeks (Special Plate, Fig. 11*b*) to one of more usual characteristics. No obvious abnormality was detected in the first sound despite the absence of mitral valve. Phonocardiography proved to be helpful in this case.

Discussion

It is outside the scope of this study to consider possible explanations of the variations in heart rate occurring immediately after birth and in the ensuing days, or the increasing incidence of systolic murmurs with age. Mechanical and chemical factors at birth, control by the autonomic nervous system, adjustments between foetal and adult circulations, and changes in basal metabolism must all be considered.

The incidence of systolic murmurs in the newborn in most previously described series has ranged between 0.5% and 5%. Siemsen (1938), however, found a 37% incidence after multiple examinations. The high percentage in the present series is probably attributable to multiple examinations, very good listening conditions, and the inclusion of very soft murmurs.

There would seem to be three possible explanations for the occurrence of systolic murmurs in this age group —congenital heart disease, persistence of blood flow through foetal channels either in the same or reverse direction, and physiological causes similar to those operating in older children.

MacMahon *et al.* (1953) gave the incidence of congenital heart disease as approximately 3 per 1,000 live births. Since the infants studied were to some extent selected, and since one is known to have congenital heart disease, it seems unlikely that any of the other murmurs are due to this cause. Some observers (Richards *et al.*, 1955; Taylor, 1953) have noted that the majority of murmurs heard in early neonatal life disappear during later infancy. Others (Keith *et al.*, 1958) have noted some persisting into early childhood and then disappearing with no evidence of cardiac abnormality. Transient murmurs were heard soon after birth in some of the infants studied, and these may have been due to the blood-flow through foetal channels. A small number of the persistent neonatal murmurs were softer at follow-up, and these may disappear later as those described above. However, it was the impression that the majority persisted unchanged at follow-up until 6 months of age.

Most of the persistent murmurs heard during the first week of life and at follow-up were not dissimilar from those described by Harris (1955) and others in normal children. Comparison of Special Plate, Fig. 8 with Fig. 8*b*, and Fig. 4*a* with Fig. 5, shows the similarity of murmurs in the two age groups. The high incidence of this type of murmur in infancy compares with that of over 90% found in normal children by McKee (1938) and Lessof and Brigden (1957). The probability is, therefore, that most of the neonatal murmurs heard persist into childhood and are functional in nature.

Because of the high incidence of systolic murmurs in normal newborn infants it is evident that the

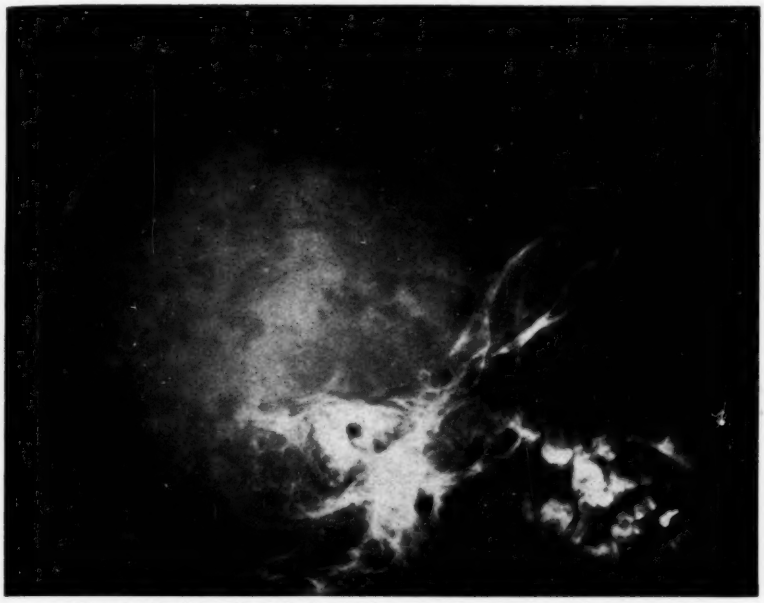


FIG. 1.—Radiograph of skull, showing extensive round translucent areas.

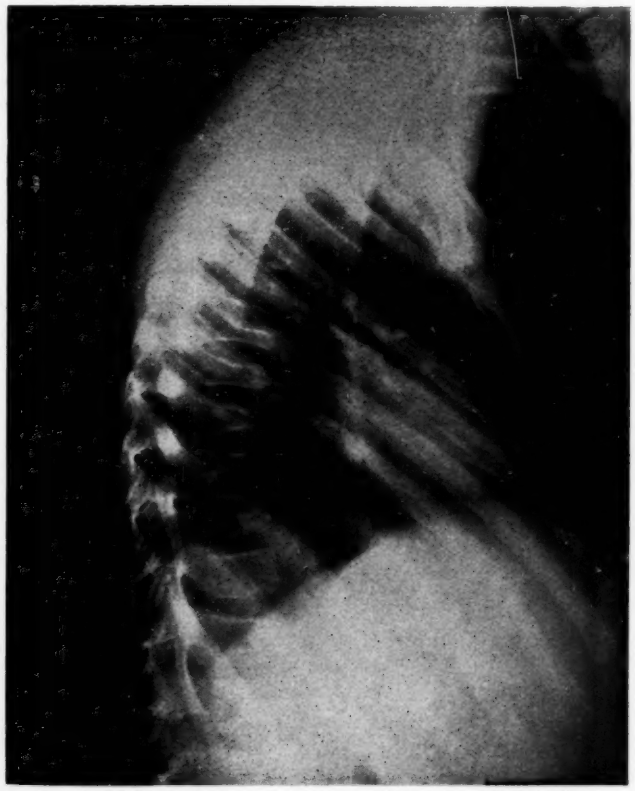


FIG. 2.—Radiograph of spine, showing collapse of vertebral bodies.

FIG. 3.—Radiograph of lower end of femur and upper end of tibia, showing translucent zones at metaphyses, large round area of translucency in tibia, spontaneous fracture, and periosteal double contour.

FIG. 4.—Radiograph of femur, showing periosteal irregularity and subperiosteal calcification.

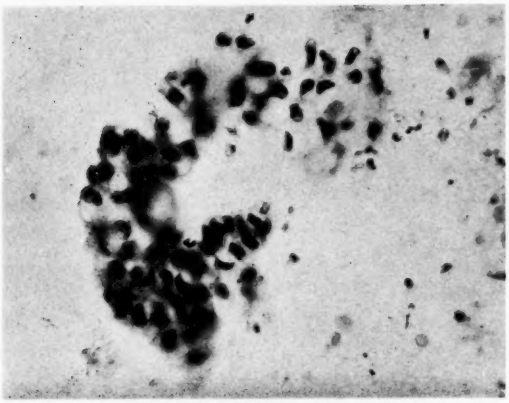


FIG. 1.—Typical clump of malignant cells present in a smear. (Papanicolaou and H. and E. ×296.)

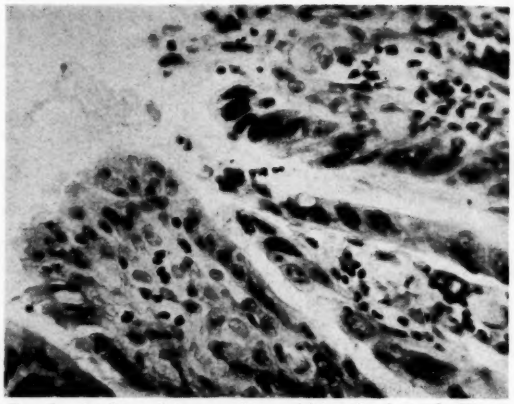


FIG. 2.—Surface of tumour from which cells shown in Fig. 1 were shed. (Papanicolaou and H. and E. ×296.)

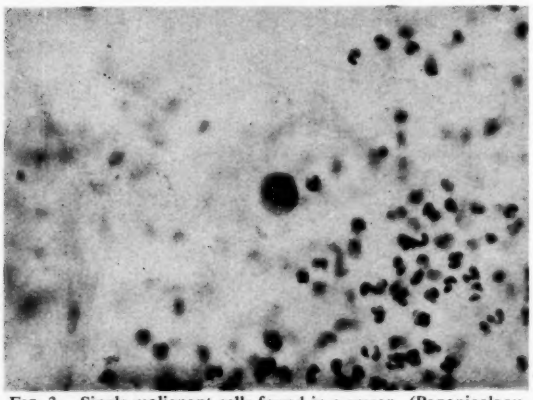


FIG. 3.—Single malignant cells found in a smear. (Papanicolaou and H. and E. ×296.)

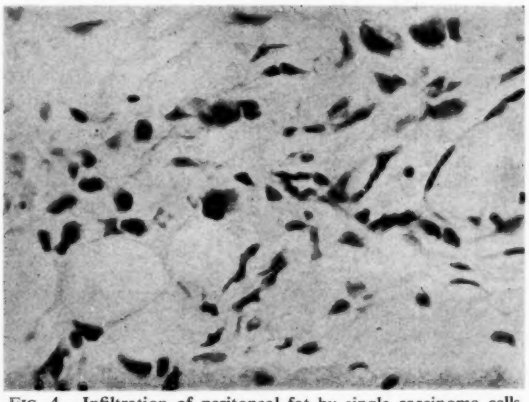


FIG. 4.—Infiltration of peritoneal fat by single carcinoma cells as seen in a biopsy from same case as Fig. 3. (Papanicolaou and H. and E. ×296.)

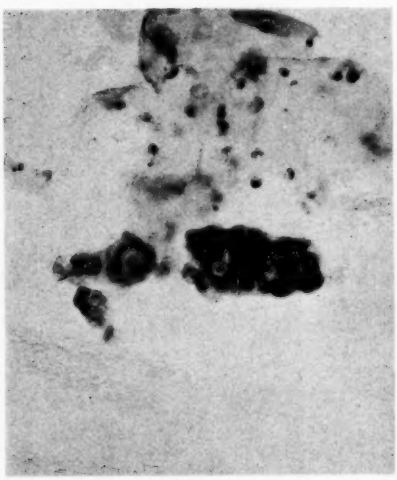


FIG. 5

FIG. 5.—Clump of malignant cells seen in a smear obtained from Case 34. (Papanicolaou. ×296.)

FIG. 6.—Small sessile mucosal outgrowth found in gastrectomy specimen from Case 34. (H. and E. ×6.)

FIG. 6

FIG. 7.—High-power field in papillary lesion of Case 34. Epithelial cells lining acini show dedifferentiation and mitotic activity. Malignant epithelial cells are infiltrating stroma (upper right). (H. and E. ×525.)

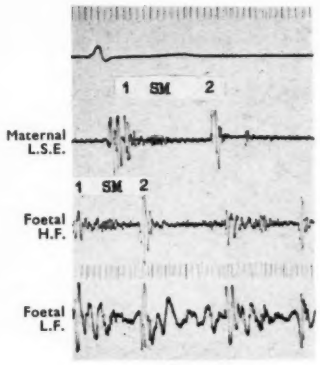


FIG. 1*a*

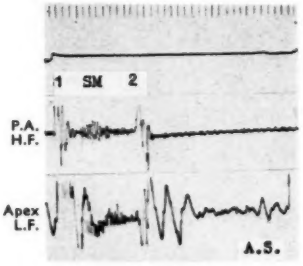


FIG. 1*b*

FIG. 1*a*. — Phonocardiogram showing maternal and foetal heart sounds, high- and low-frequency tracings. Mid-systolic murmur is demonstrated in foetal tracing.

FIG. 1*b*.—Phonocardiogram of same infant aged 5 days, showing similar type of murmur, filling sounds, and auricular sound.

[Time marker 0.01-second divisions throughout.]

FIG. 2*a*.—Phonocardiogram showing maternal and foetal heart sounds. Late systolic murmur demonstrated in foetal tracing.

FIG. 2*b*.—Phonocardiogram of same infant aged 4 days, recorded simultaneously at base and apex, showing well-amplified pulmonary component of second sound at apex and low-frequency mid-systolic murmur, clinically maximal just internal to apex.

[L.S.E.=left sternal edge; P.A.=pulmonary area; I.S.=intrascapular; L.F., M.F., H.F.=low, medium, and high frequency.]

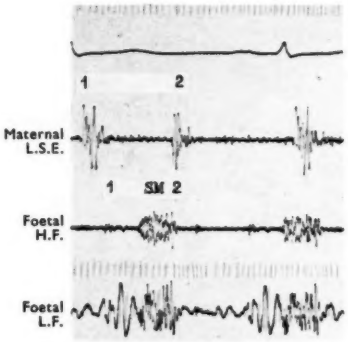


FIG. 2*a*

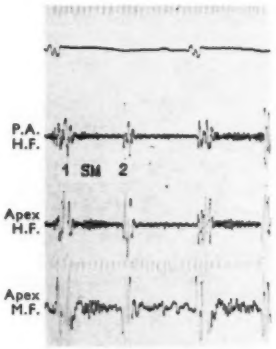


FIG. 2*b*

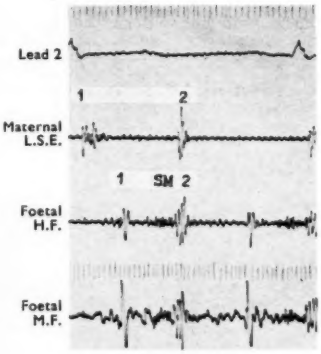


FIG. 3*a*

FIG. 3*a*.—Phonocardiogram showing maternal and foetal heart sounds. Plateau mid- and late systolic murmur shown.

FIG. 3*b*.—Phonocardiogram of same infant aged 2 days, showing mid-systolic murmur which was clearly audible when first listened to two hours after birth.

FIG. 3*c*.—Phonocardiogram of same infant aged 5 months, showing similar type of murmur, clear third heart sound, and well-marked auricular sound.

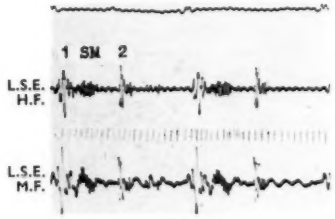


FIG. 3*b*

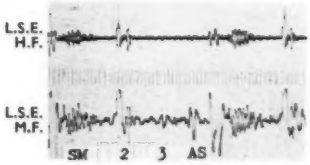


FIG. 3*c*

FIG. 4*a*

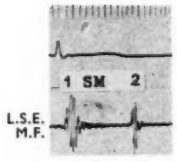


FIG. 4*b*

FIG. 4*a*.—Phonocardiogram of infant aged 4 days who had localized short high-pitched basal systolic murmur.

FIG. 4*b*.—Phonocardiogram of same infant aged 5 months, showing similar character of murmur.

FIG. 5.—Phonocardiogram of normal 6-year-old boy with simultaneous recordings at base and apex. This shows pulmonary component of second sound, best at base, a clear third heart sound, and a systolic murmur comparable in character to Figs. 4*a* and 4*b*.

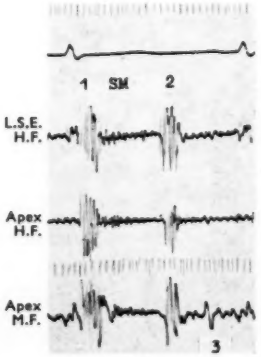


FIG. 5

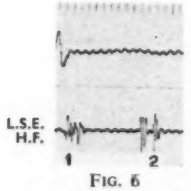


FIG. 6

FIG. 6.—Phonocardiogram of infant aged 2 days. No murmur audible or demonstrable on phonocardiogram. Clearly audible split of first and second sounds shown. Audible systolic murmur *in utero* with phonocardiogram showing murmur of type seen in Fig. 2*a*.

FIG. 7*a*

FIG. 7*b*

FIG. 7*a*.—Phonocardiogram showing characteristic "early" type of third heart sound—small and irregular in form, but occurring 0.09 second after second sound in each cycle (infant 4 days old).

FIG. 7*b*.—Phonocardiogram of same infant aged 5 months, showing better defined (though still inaudible) third heart sound 0.09 second after second sound.

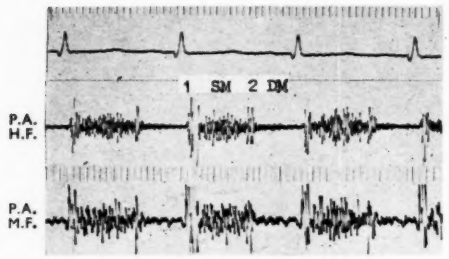


FIG. 10

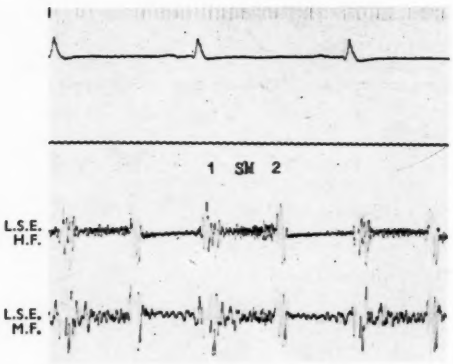


FIG. 11*a*

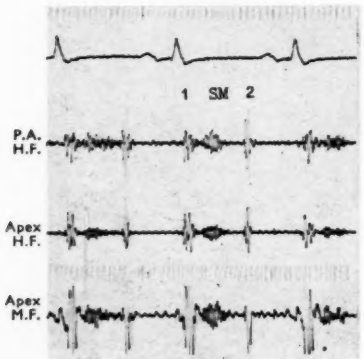


FIG. 11*b*

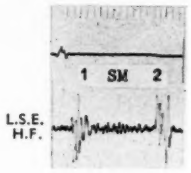


FIG. 8*a*

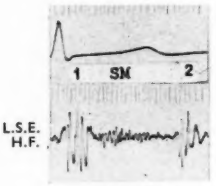


FIG. 8*b*

FIG. 8*a*. — Phonocardiogram of infant 6 hours old, showing mid-systolic murmur.

FIG. 8*b*. — Phonocardiogram of normal boy aged 11 years, showing systolic murmur comparable in character to that shown in Fig. 8*a*.

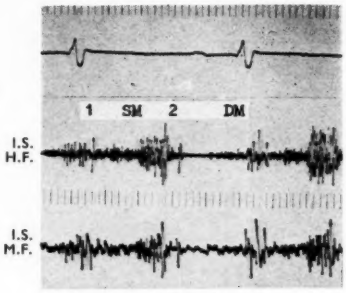


FIG. 9*a*

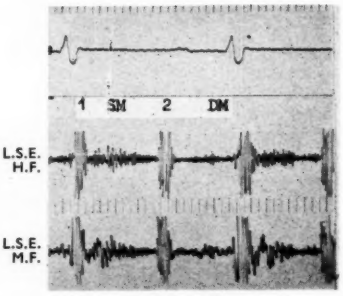


FIG. 9*b*

FIG. 9*a*.—Phonocardiogram taken at intrascapular area in infant aged 2 weeks, showing crescendo systolic murmur and presystolic murmur.

FIG. 9*b*.—Phonocardiogram of same infant recorded at third left intercostal space. Shows systolic murmur and mid- and late diastolic murmur. Infant had coarctation of aorta with interventricular septal defect and patent ductus arteriosus.

FIG. 10.—Phonocardiogram of infant aged 5 weeks recorded at pulmonary area. It shows pansystolic murmur and short diminuendo diastolic murmur. This baby had a patent ductus arteriosus tied successfully at 7 months.

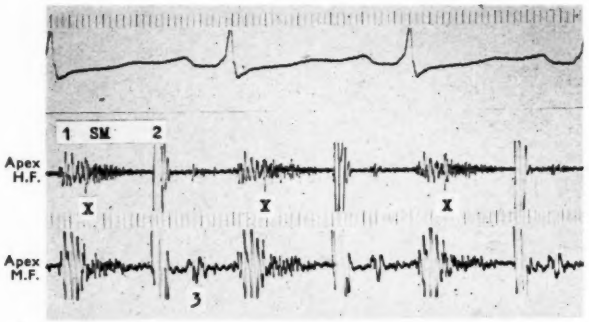


FIG. 12

FIG. 11*a*.—Phonocardiogram of infant aged 2 days, who died at 5½ weeks. It shows apparently normal first and second sounds, no obvious third heart sound, and a long-plateau systolic murmur.

FIG. 11*b*.—Phonocardiogram of same infant aged 5 weeks, now cyanosed and in heart failure. Systolic murmur is now mid-systolic in character. Post-mortem findings were of complete mitral atresia.

FIG. 12.—Phonocardiogram of a 14-month-old infant in congestive cardiac failure; the precise defect has not yet been determined. The tracing shows an ejection sound (X) and abnormally intense third heart sound. The character of the systolic murmur shown confirmed the clinical impression that it was not dissimilar to those heard in many normal infants. The same murmur was heard and recorded at the left sternal edge.

character of this murmur, that of the heart sounds, and the presence or absence of a diastolic murmur are important in deciding whether or not the heart is normal. From the present findings the characteristics of presumed functional systolic murmurs may be defined, but a murmur with apparently similar characteristics may occur in congenital heart disease or none may be audible. It is worth noting that no very loud, long, or high-pitched systolic murmurs were heard or recorded in the normal infants studied, nor any diastolic murmurs.

Foetal murmurs have been previously recorded on infants subsequently found to have congenital heart disease (Smith and Hervert, 1940 ; Smith, 1941 ; Menzies and Scott, 1955). The present findings show that murmurs may be recorded in the majority of foetuses near term, and may be audible by foetal stethoscope without a congenital defect being present.

Summary and Conclusions

A series of 230 full-term infants were examined daily from birth for a minimum of eight days, and observations made on sleeping heart rate, sounds, and murmurs. A quarter of this number were re-examined between the ages of 6 weeks and 6 months. Phonocardiograms were taken on an approximate quarter of the series both before and after birth, and also on a number of infants with known congenital heart disease. From these observations some normal auscultatory data in early infancy could be obtained.

The mean sleeping heart rate was tabulated, and showed a significant rise from the second to the eleventh day. All murmurs heard were systolic in timing, and their incidence increased with age, reaching 77% by the eighth day and nearly 90% at follow-up examination. The characteristics of these murmurs could be broadly defined, both clinically and phonocardiographically. It is suggested that the majority probably persist into childhood and are functional in nature.

Deviations from the expected normal may be detected clinically, but, because of the difficulties of auscultation, phonocardiography may be a particularly useful diagnostic aid in this age group.

The demonstration of systolic murmurs in the majority of foetal tracings implies that the chance observation of an intrauterine murmur does not necessarily imply that the infant has congenital heart disease.

I should like to thank Mr. D. M. W. Maxwell and Dr. J. J. Kempton for permission to study their patients and for their encouragement. I am most grateful to Professor E. G. L. Bywaters, Dr. W. W. Brigden, and Dr. G. T. Thomas for their criticism, and am indebted to Dr. E. J. Holborow for statistical aid and to Mr. J. K. Harrison for technical assistance. I should also like to thank the nursing staff of the midwifery department and Mrs. A. M. Caulkin for their unfailing help.

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INCIDENCE OF LEUKAEMIA IN SINGAPORE, AND RARITY OF CHRONIC LYMPHOCYTIC LEUKAEMIA IN CHINESE

BY

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The aetiology of human leukaemia is still largely obscure, and therefore variations in the incidence of leukaemia in different population groups are especially interesting because of their potential aetiological significance. The only Asian population for which reliable leukaemia mortality figures have previously been available is that of Japan, where the mortality from leukaemia in both sexes and in all age-groups is much less than that of countries in Europe and North America (World Health Organization, 1955). Several authors have also mentioned the clinical impression that chronic lymphocytic leukaemia is particularly uncommon in the tropics generally (Strong, 1944), in India (Majumdar and Chatterjee, 1953), in Japan and the indigenous population of North and South Africa (Witts, 1957), and in Singapore (Wells, 1958). The predominantly Chinese population of Singapore has had comprehensive and effective medical care since the end of the Japanese occupation, and we have analysed the incidence of leukaemia here during the ten-year period 1949–58.

Data and Material

We have examined all the Singapore death certificates and post-mortem reports for the 1949–58 period in which leukaemia or lymphosarcoma are mentioned as a diagnosis or cause of death. Over 95% of these certificates and reports refer to patients investigated at the Singapore General Hospital, in the University departments of medicine and clinical medicine, or in the paediatric unit. We have re-examined the diagnostic criteria of 129 patients with leukaemia attending the department of medicine in the 1949–58 period, many of whom were treated by one or other of us, and have also obtained additional clinical data on some of the patients who attended the paediatric unit. After correlation of all these data and elimination of duplicate and doubtful records, we have records of 253 cases of leukaemia and 23 of lymphosarcoma from the 1949–58 period.

Population figures have been obtained by extrapolation from the 1947 and 1957 Singapore Census reports and the Annual Reports of Singapore Births and Deaths.

Crude Leukaemia Mortality Rates

The number of deaths from leukaemia in Singapore in each of the 10 years 1949–58, together with the crude mortality rates, are given in Fig. 1. The figures for Chinese are given separately.

During the ten years under investigation there has been expansion of the Singapore Medical Services, with improved laboratory and diagnostic facilities, and at the same time the Chinese and other Asians in Singapore

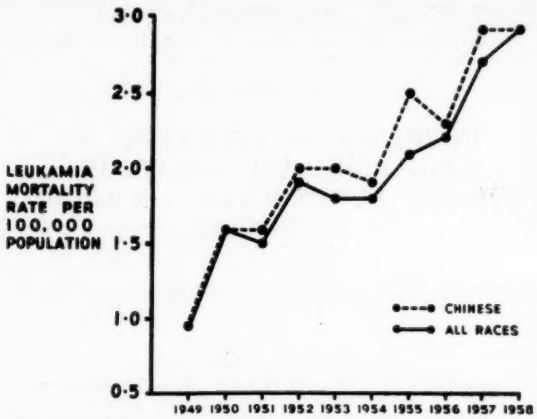

FIG. 1.—Crude yearly mortality rates from leukaemia in Singapore, 1949–58.

have shown an increasing acceptance of Western medicine. These factors undoubtedly explain much of the apparent increase in the crude mortality rate from leukaemia. Many Asians, particularly the Chinese and Malays, prefer to leave hospital when in the terminal stages of a fatal illness, to die at home. Some patients in this series, known to have had leukaemia, have died at home, and their death certificates sometimes record other causes of death, or simply "death from natural causes." Thus in this series of 253 cases of leukaemia, only 206 had this diagnosis on their death certificates. The remaining 47 were mostly diagnosed and treated in the department of medicine: 38 of them are known to have died by the end of 1958; the other 9 cannot be traced, and are thought to have died. We estimate that about another 50 patients with leukaemia were probably diagnosed similarly in the department of clinical medicine and the paediatric unit at the General Hospital, and later their deaths were not recorded as being due to leukaemia. They will not have been included in this series.

The above figures suggest that the numbers of deaths from leukaemia shown in Fig. 1 represent about 80% of the cases actually diagnosed in Singapore.

In recent years about 75% of all deaths registered in Singapore have had the causes of death certified by registered medical practitioners or coroners. The remainder have been certified by the police. We believe that a more accurate comparison can be made between the mortality rates from leukaemia in Singapore and those reported in other countries (see Table I, compiled from data given by the World Health Organization, 1955) if our figures in this series are increased by 33% (see Table II).

TABLE I.—*Mortality From Leukaemia in 17 Countries, 1950–2. Mean Annual Rates per 100,000 Population*

Males	Countries	Females
7·0–7·5	United States (White), Denmark	5·0–5·4
6·0–6·9	Sweden, Norway, New Zealand	
5·0–5·9	Switzerland, Canada, Netherlands, Australia	4·0–4·9
4·0–4·9	England and Wales, Scotland, Germany, France, Italy	3·0–3·9
3·0–3·9	Finland, United States (non-Whites), Ireland	2·0–2·9
2·0	Japan	1·5

TABLE II.—*Mortality From Leukaemia in Singapore, 1957–8 (Figures in This Series, and Estimated (Comparable With Table I) Mean Annual Rates per 100,000 Population)*

	All Races		Chinese	
	Males	Females	Males	Females
Present series ..	3·6	1·9	3·8	2·0
Estimated ..	4·8	2·5	5·1	2·7

Sex Incidence

The sex incidence of the 253 cases of leukaemia is summarized in Table III, and the mean annual mortality rates for Chinese males and females at different ages are shown in Fig. 4. Leukaemia is commoner in men than in women in many countries (see Table I) and at all ages (see Fig. 2, drawn from data given by the World Health Organization, 1955). Our figures are in general agreement with this finding, but we feel that the preponderance of leukaemia in the males is probably exaggerated in our series because there are better medical facilities for men than for women in Singapore, and men appear to be less reluctant here than women in seeking medical treatment.

The sex ratio obtained for Chinese males to females is 2:1, approximating to the similar sex ratio of the mean annual mortality rates. The sex ratios for the

TABLE III.—*Sex Incidence of 253 Cases (171 Male, 82 Female) of Leukaemia*

	Males	Females		Males	Females
Chinese ..	135	68	Europeans ..	4	1
Indians ..	19	4	Eurasians ..	1	1
Malays ..	10	7	Others ..	2	1

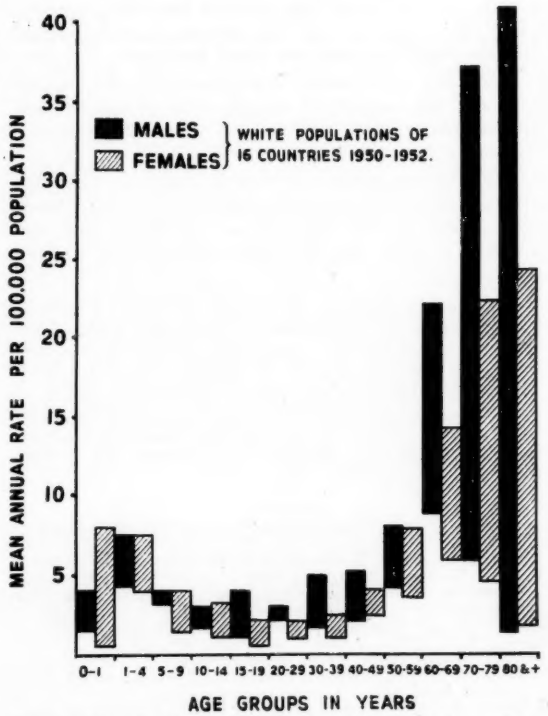

FIG. 2.—Mortality from leukaemia in white populations. (The vertical columns represent the ranges reported in 16 countries, 1950–2).

TABLE IV.—*Classification of 253 Cases of Leukaemia and 23 of Lymphosarcoma in Singapore*

	Leukaemic	Subleukaemic	Aleukaemic	Unknown	Total
Chinese (203)					
Granulocytic:					
Acute	18	6	—	17	41
Subacute	4	1	—	—	5
Chronic	26	1	1	12	40
Unknown	—	—	—	5	5
Lymphocytic:					
Acute	8	4	2	10	24
Subacute	1	—	1	—	2
Chronic	2	1	—	—	3
Unknown	—	—	—	3	3
Lymphosarcoma (19):					
Monocytic:					
Acute	3	—	—	—	3
Unknown:					
Acute	2	—	1	44	47
Subacute	—	—	—	3	3
Unknown	1	—	8	18	27
Indians (23)					
Granulocytic:					
Acute	—	1	1	2	4
Subacute	1	—	—	—	1
Chronic	4	—	—	2	6
Unknown	—	—	—	1	1
Lymphocytic:					
Acute	1	1	1	2	5
Unknown:					
Acute	—	—	—	4	4
Unknown	—	—	—	2	2
Malays (17)					
Granulocytic:					
Acute	2	—	—	2	4
Chronic	2	—	—	1	3
Lymphocytic:					
Acute	1	—	—	2	3
Unknown:					
Acute	—	—	—	2	2
Unknown	—	—	1	4	5
Eurasians (2)					
Granulocytic, chronic	1	—	—	—	1
Lymphosarcoma (2):					
Unknown:					
Unknown	—	—	—	1	1
Europeans (5)					
Granulocytic:					
Acute	1	—	—	—	1
Chronic	1	1	—	—	2
Lymphosarcoma (2):					
Unknown:					
Acute	—	—	—	2	2
Others (3)					
Granulocytic:					
Acute	—	—	—	1	1
Chronic	1	—	—	—	1
Unknown:					
Unknown	—	—	—	1	1

Indians and Europeans are largely explained by the preponderance of males in these respective populations.

Age Incidence

The proportion of young people in the populations of the Far East is much higher than in white populations in Europe and North America, and since mortalities from leukaemia in the latter are higher in the older age-groups (see Fig. 2), comparisons of crude mortality rates for these different populations may be misleading. The population structure in Singapore, derived from census returns in 1947 and 1957, is shown in Fig. 3. Chinese mortality rates from leukaemia in different age-groups, based on 202 cases in this series, are shown in Fig. 4. (The age of one Chinese patient with leukaemia is unknown.)

Type Incidence of Leukaemia

We have classified the 253 cases of leukaemia and 23 cases of lymphosarcoma in this series in Table IV, in accordance with the recommendations of the Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-forming Organs (1950), except that we have retained the use of the term "lymphosarcoma," which is still generally used in preference to the recommended term "lymphocytic

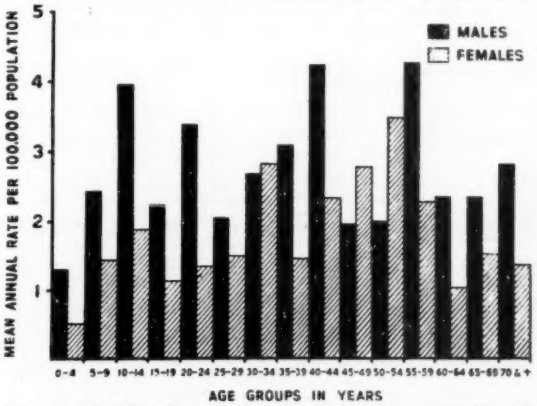

FIG. 4.—Mortality from leukaemia in Chinese population of Singapore, 1949–58.

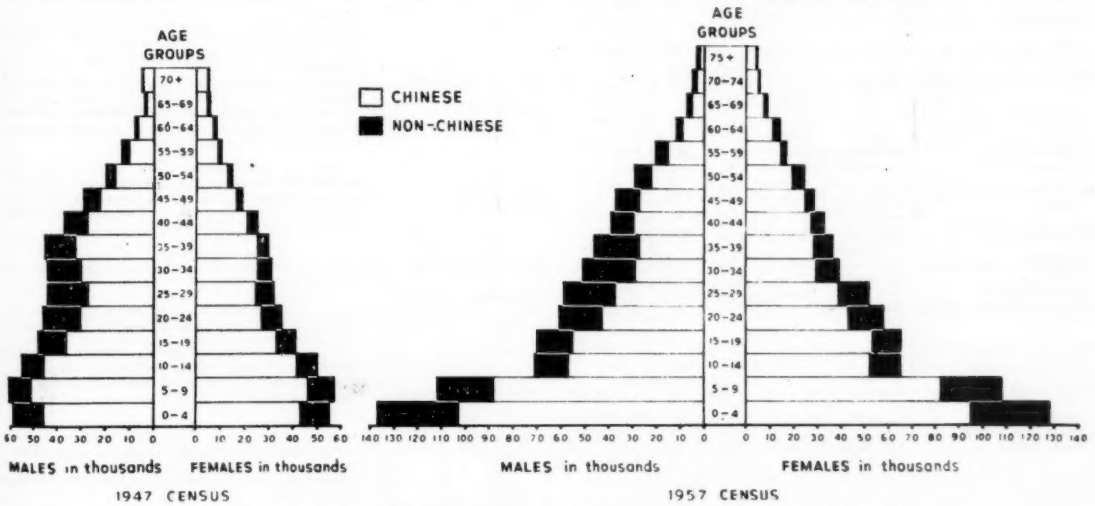

FIG. 3.—Age distributions of Singapore Chinese and non-Chinese populations, 1947 and 1957.

TABLE V.—*Incidence of the Various Types of Leukaemia in Different Population Groups*

References	Regions	No. of Cases Analysed	Incidence of Leukaemia						Remarks
			Chronic		Acute and Subacute			All Acute, Subacute and Monocytic	
			Lymphocytic	Granulocytic	Lymphocytic	Granulocytic	Monocytic		
Ward (1917)	Many countries	729	12%	34%	—	—	—	55%	
Panton and Valentine (1929)	London	172	15%	52%	—	—	—	34%	
Gardikas *et al.* (1955)	England	Almost 1,000	30%	30%	—	—	—	—	No data on acute forms of leukaemia
Scott (1957)	London	169	—	—	—	—	—	—	The 169 cases of acute, subacute and monocytic leukaemia include 5 erythraemias, 57 acute, subacute, and lymphocytic, 84 granulocytic, and 23 monocytic leukaemias. No data on chronic forms
Gauld *et al.* (1953)	Scotland	647	32%	26%	22%	11%	9%	42%	
Husebye and Gaustad (1956)	Oslo, Norway	122	16%	21%	—	—	—	63%	
Nordenson and Asplund (1956)	Sweden	1,548	38%	9%	3%	21%	2%	53%	821 acute, subacute, and monocytic leukaemias include 221 stem-cell leukaemias and 190 "paraleukäemien." These figures exclude 187 "retikulosen"
Gram and Nielsen (1932)	Denmark	300	37%	35%	3%	3%	—	29%	86 acute leukaemias include 66 with cell type undifferentiated; 300 total excludes 3 aleukaemic granulocytic leukaemias and 241 other leukaemias (7 aleukaemic) all not further differentiated
Videbaek (1947)	Copenhagen, Denmark	310	41%	25%	—	—	1%	34%	
Donner and Maly (1954)	Prague, Czechoslovakia	539	32%	36%	—	—	—	32%	
Alfieri and Capone (1954)	Rome, Italy	244	20%	33%	13%	11%	2%	40%	244 cases include 14 "istioleucaemia" and 1 basophil leukaemia. 98 acute, subacute, and monocytic leukaemias include 36 erythraemias
Ruol and Corsi (1954)	Padua, Italy (adults)	305	27%	30%	11%	9%	2%	42%	128 acute, subacute, and monocytic leukaemias include 61 "emocitoblastiche" and 2 "eritroleucemie." 305 total cases also include 2 chronic "istioleucemie" and 1 chronic "eritroleucemie." These figures exclude 2 acute "reticulo-istiocitarie," 12 acute and subacute, and 20 other leukaemias, all not further differentiated
Rosenthal and Harris (1935)	New York, U.S.A.	455	23%	35%	7%	29%	33%	40%	160 cases of chronic granulocytic leukaemia include 3 eosinophil leukaemias, 15 cases of monocytic leukaemia, 6 "aleukaemic leukaemias"; 455 total cases also includes "6 myelocytic and 4 polynuclear cell leukaemias associated with polycythaemia"
Rosenthal (1954)	New York, U.S.A.	479	22%	18%	3%	45%	13%	60%	These figures exclude 7 plasma-cell and 3 reticulum-cell leukaemias, and other cases of myelofibrosis, myelomatosis, and follicular lymphoblastoma
Leavell (1938)	New York, Boston, and Philadelphia, U.S.A.	478	27%	38%	—	—	—	—	No data on acute forms
MacMahon and Clark (1956)	Brooklyn, U.S.A. (white)	1,516	26%	21%	9%	31%	5%	52%	Excludes 41 lymphocytic, 48 granulocytic, 3 chronic, 2 others, and 26 unknown types of leukaemia, all not further differentiated
Kirshbaum and Preuss (1943)	Cook Co., U.S.A. (white)	94	24%	17%	11%	27%	3%	59%	55 acute, subacute, and monocytic leukaemias include 17 acute stem-cell leukaemias; these figures exclude 2 "chronic aleukaemic stem-cell leukaemias"
Latourette *et al.* (1954)	Michigan, U.S.A.	777	29%	31%	12%	10%	18%	40%	81 acute and subacute granulocytic leukaemias include 8 subacute "myelo-monocytic" leukaemias. These figures exclude 2 "leukaemia cutis" and 148 leukaemias not further differentiated
Sacks and Seeman (1947)	Baltimore, U.S.A.	92	22%	18%	27%	28%	4%	60%	These figures exclude 21 lymphocytic and 21 myeloid (chronicity not stated) and 20 leukaemias (not further differentiated)
Wintrobe (1951)	Baltimore, U.S.A. (white)	142	33%	35%	—	—	—	32%	
Bethell (1943)	Michigan, U.S.A.	415	19%	37%	14%	21%	10%	44%	153 chronic granulocytic leukaemias include 22 chronic "myelo-monocytic" leukaemias; 86 acute and subacute granulocytic leukaemias include 46 acute "myelo-monocytic" leukaemias; 40 "histiomonocytic" leukaemias included as monocytic leukaemia
Best and Limarzi (1952)	Chicago, U.S.A.	851	33%	25%	8%	18%	5%	42%	360 cases of acute, subacute, and monocytic leukaemia include 105 acute leukaemias (not further differentiated). These figures exclude 41 reticulum-cell and 3 plasma-cell leukaemias and 21 cases of lymphosarcoma in a leukaemic phase
Rubnitz (1952)	Nebraska, U.S.A.	100	25%	37%	—	—	—	38%	
Steinkamp (1954)	St. Louis, U.S.A.	548	—	—	—	—	—	—	No data on acute forms. 302 cases of chronic lymphocytic and 246 chronic granulocytic leukaemias
Kirshbaum and Preuss (1943)	Cook Co., U.S.A. (coloured)	27	11%	15%	4%	30%	7%	74%	20 acute, subacute, and monocytic leukaemias include 9 acute stem-cell leukaemias. These figures include 1 Chinese monocytic leukaemia
Wintrobe (1951)	Baltimore, U.S.A. (coloured)	21	33%	43%	—	—	—	24%	
MacMahon and Clark (1956)	Brooklyn, U.S.A. (coloured)	70	17%	26%	23%	23%	4%	57%	Excludes 2 lymphocytic and 1 chronic leukaemia, all not further differentiated
Rosenfeld (1955)	Sao Paulo, Brazil	273	11%	27%	—	—	—	62%	
Gunz and Hough (1956)	New Zealand	523	15%	19%	25%	25%	1%	66%	346 cases of acute, subacute, and monocytic leukaemia include 77 with no data on cell type. These figures exclude 8 lymphocytic and 6 granulocytic (chronicity not stated), 9 chronic leukaemias (not further differentiated), and 7 others (no further data given)
Earle (1943)	Samoa	7	—	—	43%	57%	—	100%	Excludes 1 myeloid leukaemia (acute or chronic not stated)
Chatterjea (1958)	Calcutta, India	252	6%	38%	18%	25%	10%	54%	
Hibino *et al.* (1958)	Japan	321	1%	62%	32%	—	4%	36%	
Present series	Singapore (Chinese)	168	2%	24%	15%	27%	2%	74%	125 acute leukaemias include 50 with cell type undifferentiated; 168 total excludes 5 granulocytic, 3 lymphocytic, and 27 other leukaemias, all not further differentiated

sarcoma." We have listed lymphosarcoma in Table IV immediately below the lymphocytic leukaemias to emphasize the close relationship between lymphosarcoma and chronic lymphocytic leukaemia. The only definitive distinction between the two conditions appears to be that lymphosarcomas (lymphomas) " are not characterized by diffuse marrow dissemination early in their course " (Committtee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-Forming Organs, 1950), a distinction which we have sometimes been quite unable to make in retrospect. If chronic lymphocytic leukaemia and lymphosarcoma are in fact only slightly different manifestations of the same condition, the relative rarity of the former in the Far East would have less aetiological significance if compensated by a relatively greater number of lymphosarcomas.

However, even if the cases of lymphosarcoma in our series are added to those of chronic lymphocytic leukaemia, the proportional incidence of the two together in the Chinese population is still far less than that of chronic lymphocytic leukaemia in white populations (see Table V), and the mortality in the older age-groups of Chinese is not greatly altered (see Table VI). The highest proportions of chronic lymphocytic leukaemia have been reported from Scandinavia, with successively lower proportions in other white populations, in American coloured populations, in Indians, and in Japanese, Chinese (present series), and Samoans (see Table V).

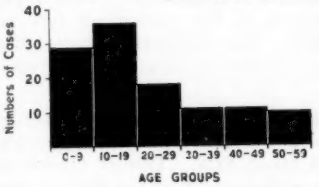

FIG. 5.—Age distribution of 115 cases of acute leukaemia in Singapore Chinese.

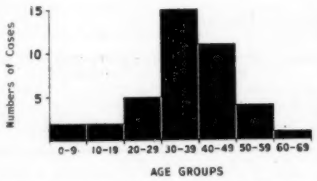

FIG. 6.—Age distribution of 40 cases of chronic granulocytic leukaemia in Singapore Chinese.

The commonest type of leukaemia in Singapore Chinese is acute leukaemia (all cell types), accounting for 68% of cases. This appears to be the commonest form of leukaemia in younger age-groups all over the world, and the Singapore incidence is therefore to be expected because of the high proportion of young people in our population. The age distribution of 115 cases of acute leukaemia in Singapore Chinese is given in Fig. 5, showing a peak distribution in the 10–19 age-group, and contrasts with the age distribution of 40 cases of chronic granulocytic leukaemia in the same population, showing a peak in the 30–39 age-group (see Fig. 6).

TABLE VI.—*Mortality Rates in Different Age-groups of Chinese From Leukaemia and Lymphosarcoma.* (*Rates per* 100,000 *Population*)

Age-groups in Years	Leukaemia Alone		Leukaemia and Lymphosarcoma	
	Males	Females	Males	Females
<5	1·31	0·53	1·31	0·53
5–9 ..	2·40	1·44	2·53	1·44
10–14 ..	3·96	1·86	4·34	2·07
15–19 ..	2·24	1·11	2·24	1·11
20–24 ..	3·38	1·35	3·90	1·35
25–29 ..	2·06	1·49	2·65	1·49
30–34 ..	2·69	2·84	3·03	2·84
35–39 ..	3·10	1·47	3·44	1·47
40–44 ..	4·25	2·35	4·60	2·74
45–49 ..	1·96	2·80	2·35	3·26
50–54 ..	2·00	3·49	2·25	4·65
55–59 ..	4·29	2·31	4·29	2·31
60–64 ..	2·38	1·05	2·38	2·10
65–69 ..	2·38	1·54	4·74	1·54
70+ ..	2·83	1·38	2·83	1·38

Summary

A total of 253 cases of leukaemia known to have occurred in Singapore during the 10-year period 1949–58 are analysed. In the last two years of this period the reported mortality from leukaemia was 3.6 per 100,000 males per annum, and 1.9 per 100,000 females per annum. The mortality rates from leukaemia in Singapore are compared with those reported from 17 other countries.

The rarity of chronic lymphocytic leukaemia is confirmed in Chinese, this form accounting for only 3 out of 203 cases of leukaemia in Singapore Chinese. This finding is compared with the proportional incidence of the commoner forms of leukaemia reported in several other countries.

We are grateful for the help and co-operation we have received from Professor G. A. Ransome (department of medicine), Professor T. A. Lloyd Davies (department of social medicine), Professor R. Kirk (department of pathology), Dr. L. S. da Silva (senior Government pathologist), Dr. K. Shanmugaratnam (senior clinical pathologist), Dr. E. Field (physician in charge of the paediatric unit), Mr. Choo Kim Hock (registrar of births and deaths), and Mr. E. J. Phillips (chief Government statistician).

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RECURRENT MIKULICZ'S APHTHAE TREATED WITH TOPICAL HYDROCORTISONE HEMISUCCINATE SODIUM

DOUBLE-BLIND CONTROLLED CLINICAL TRIAL

BY

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The favourable report of the use of topical hydrocortisone hemisuccinate in recurrent aphthae by Truelove and Morris-Owen (1958) was thought to be encouraging enough to merit a controlled trial of this form of treatment.

Method and Material

A double-blind controlled clinical trial has therefore been undertaken to assess the relative value of tablets containing 2.5 mg. of hydrocortisone hemisuccinate with a lactose base, and an inert preparation of the lactose base alone, to patients suffering from these ulcers.

Patients were given four tablets a day to take when the ulcers were present and two tablets a day when they were not, and were asked to allow the tablets to dissolve in the region of the ulceration. This meant that most patients were, in fact, taking four tablets a day, apart from four patients who had complete remissions and who then took only two a day.

The trial involved 17 patients (8 male, 9 female) all with a long history of the same type of severe recurrent oral ulceration, often known as Mikulicz's aphthae (Prinz and Greenbaum, 1939). This type of ulceration is common, with the ulcer beginning clinically as a thickening of the non-keratinized mucosa, which within 24 hours breaks down into an ulcer without any vesicular stage. The site is determined largely by trauma, and is commonly the lower lip, commissures, buccal sulci, or the lateral margins of the tongue. It is unusual for more than four ulcers to be present at any one time, and most ulcers last from 8 to 12 days. Only long-standing ulcers heal with a scar. The ulcer is often 0.5–1 cm. in diameter, and has a punched-out, crater-like appearance with raised red rampart-like margins. In four patients a small ulcer was removed for histological examination, and in each case the diffuseness of the chronic inflammatory reaction in the corium and the absence of any change in the bordering epithelium suggest that the lesion may begin in the corium rather than in the epithelium.

In this type of ulceration natural remissions are common, and a good response is often given to any form of new treatment. Some patients known to have had these aphthae five years previously were recalled and were found to be free from ulcers. The trial was restricted to patients with almost continuous ulceration; those with multiple shallow herpetiform erosions were excluded. Two patients had a complete remission a few weeks before the trial began and could not be included. None of the patients experienced ulceration in other parts of the body.

Each patient was given a specially designed form on which to keep a written record of the time each ulcer lasted, its site, and its relative size during the trial. At the start every patient kept the record for at least a month, and then was allotted tablets A or B from a list of random numbers. During the trial it was not known either to patients or to investigators which of the two tablets contained the hydrocortisone hemisuccinate. The patients were told that two preparations were being tested. The trial periods were of eight weeks, with an intervening period of two weeks without treatment. If during the first half of the trial patients were using tablets A, then they had tablets B during the second half, and vice versa.

Analysis and Results

Two figures lent themselves to accurate measurement—namely, the number of new ulcers and the number of ulcer days in a given period. By ulcer days is meant the sum of the duration of all ulcers during the period—for example, two ulcers occurring at the same time and each lasting a week are recorded as 14 ulcer days. This unit gives a measure of the amount of distress experienced by the patient. The results are shown in the Table and (for the mean number of ulcer days per week) in Fig. 1.

There was a much better clinical response to the drug than to the inert tablet, the difference being greater when the placebo was taken first. During treatment by the drug there is a reduction of about 50% in the number of ulcer days and in the number of new ulcers compared with the placebo. These differences are highly significant.

Results of Treatment

Order	No. of Patients	Placebo A	Drug B	Difference between Means, with Standard Error
Ulcer days per 8-weeks period (mean values)				
AB ..	8	83·8	23·1	60·6 ⎫ Difference (AB v. BA)
BA ..	9	50·0	29·1	20·9 ⎭ = 39·7 ± 17·4*
Total	17	65·9	26·3	39·6 ± 9·8†
Total ulcers per 8-weeks period (mean values)				
AB ..	8	11·88	3·75	8·12 ⎫ Difference (AB v. BA)
BA ..	9	6·44	4·44	2·00 ⎭ 6·12 ± 2·77*
Total	17	9·00	4·12	4·88 ± 1·54†

* Significant at the 5% level. † Significant at the 1% level.

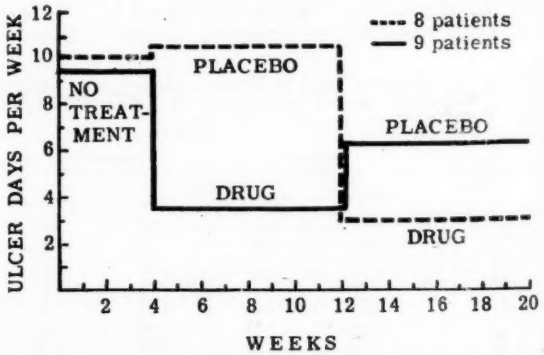

FIG. 1.—Mean ulcer days per week. Because a few patients forgot to give themselves a two-weeks "no treatment" period between the two halves of the trial period, this has been omitted from the chart.

Four patients experienced complete remissions, three while being treated with the drug and one while on the placebo. Seven other patients had only 7 to 10 ulcer days during the whole eight-weeks period while taking the active tablets.

Apart from the relief of pain given by the reduction of ulceration, the impression was not gained that the individual ulcers were any the less painful while the active tablets were being taken. Figures relating to the size of the ulcers were too subjective for accurate evaluation, but in almost every case the ulcers were smaller while the active tablets were being taken.

Progress

After the trial was over, all the patients, apart from one who did better on the placebo, were told that the tablets that had given them the greatest benefit contained 2.5 mg. of hydrocortisone hemisuccinate and that they were marketed under the trade name of "corlan." Thereafter, corlan tablets were prescribed in varying maintenance doses. The patient who had a complete remission on the placebo has maintained the remission on the placebo tablets for four months. Of the other three patients in whom the active tablets were thought to have produced a complete remission, in two the remission has been maintained for three months without treatment, and in the other the remission has been maintained for three months on corlan tablets.

Nine patients had a period of about a month without treatment after the trial: in six of them the ulcers quickly returned to their normal severity, in two the ulceration was less severe, and one had a complete remission. Thereafter the patients have been three months on varying maintenance doses of two, three, and four corlan tablets a day with effect similar to that achieved on the trial. The response to maintenance therapy varied from patient to patient, and even four tablets a day did not prevent exacerbations.

The varying response in three patients is of interest.

Case 1.—A woman of 21 gave a seven-years history of severe recurrent ulceration. This continued at the same severity through the trial period without treatment and on the placebo (Fig. 2), but while on the drug she suffered only a third as much. Then followed a seven-weeks period without treatment, during which time the ulceration returned to its former severity. She was then told that she was to be put on the active preparation—namely, corlan tablets, four a day—and the effect for a month was exactly the same as during the period when, unknowingly, she had been receiving the same treatment. On smaller doses the treatment was less effective, but, even so, there was still a marked reduction of about 50% in ulcer days.

Case 2.—A man aged 29 gave a 16-years history of severe recurrent ulceration. After his preliminary period without treatment he was placed on the active preparation with about 25% relief of the ulceration, but while on the placebo he had a severe exacerbation of the ulcers (Fig. 3).

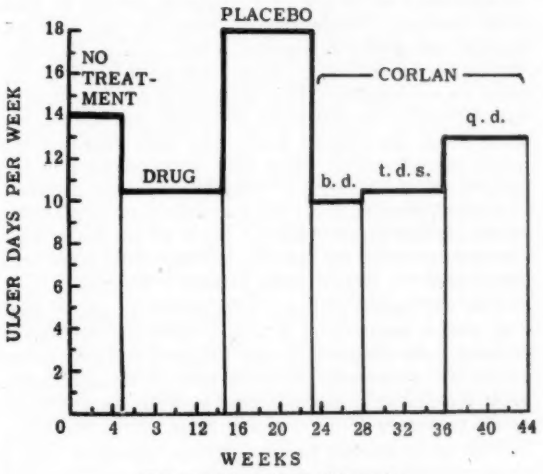

FIG. 3.—Ulcer chart of Case 2.

Then he was given corlan tablets twice a day for eight weeks with the same effect as when he was receiving four a day on the trial. Then followed two months with corlan tablets three times a day, the effect being almost the same as with two a day. Finally he was given corlan tablets four times a day, and the amount of ulceration experienced almost returned to the pre-trial level without treatment.

Case 3.—A woman aged 27 gave a seven-years history of severe recurrent ulceration. Her ulceration was so severe that after only a three-weeks instead of the usual four-weeks preliminary period without treatment she was placed on the trial, receiving, as it happened, the active preparation first (Fig. 4). The relief was remarkable, the ulceration being only a fifth as severe as it was before. Then during the following fortnight without treatment, the ulceration

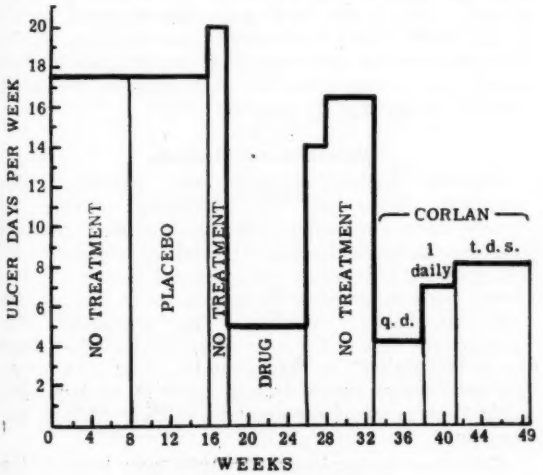

FIG. 2.—Ulcer chart of Case 1.

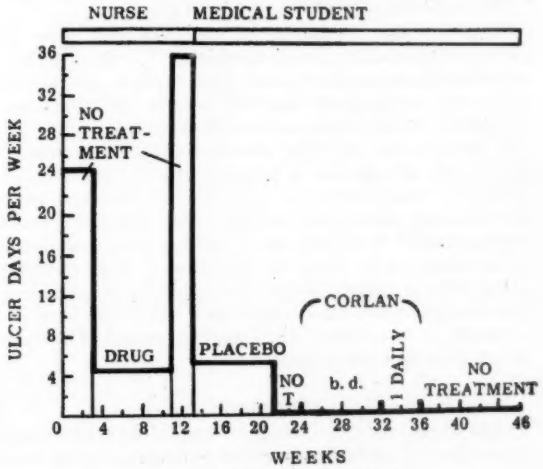

FIG. 4.—Ulcer chart of Case 3.

returned with a severe exacerbation. There followed a period on the placebo, the relief being just as great as when she had been taking the drug. The day she began taking the placebo coincided with the achievement of her life's ambition, for she began her medical studies, having previously been a nurse. She soon stopped having ulcers, and had a complete remission. This continued for six months, whether or not she was taking corlan tablets.

Discussion

The advantage of drug over placebo has clearly been demonstrated in 16 out of 17 patients serving as their own controls. When considering all the patients together the degree of ulceration was reduced by about 50%, and the reduction could often be maintained for three to six months. It is interesting to note that in Figs. 2 and 3 the effect of the drug was almost the same when the patients knew they were receiving the active preparation as when they were unaware of the nature of the tablets. Nevertheless, any complete remissions were probably the result of the natural history of the disease rather than the result of the drug, since one occurred with the placebo and two others have been maintained for three months without treatment.

That the response to the drug over a period of time was not as constant as in Fig. 3 does not necessarily mean that the drug is no longer effective, but may rather reflect the periodicity of the severity of the ulceration, as is also shown by the difference between the ulceration at the beginning of the trial and while on the placebo.

That psychological factors play an important part is suggested not only by the difference between the effect when the active preparation preceded the placebo and vice versa, but in the history in Case 3, illustrated by Fig. 4, when the remission is plainly not the result of any therapy but perhaps the personal satisfaction of beginning medical studies. The smaller effect of the active preparation over the inactive one when the former was given first can also be accounted for by the feeling of well-being that these patients experience when at last they obtain some relief, even though only partial, from their severe ulceration.

No side-effects have been noted in patients treated in this way, but it has been my experience, so far, that only the Mikulicz type of ulceration responds in this manner, and that the type of recurrent ulceration with multiple shallow erosions of herpetiform type is made worse, not better, by local hydrocortisone therapy.

Thus in the treatment of the Mikulicz type of recurrent ulceration, tablets containing 2.5 mg. of hydrocortisone hemisuccinate given four times a day are of value in reducing by half the degree of ulceration, especially during acute exacerbations. Remissions are not induced nor are they maintained by the treatment in the type of case that is severe enough to warrant this therapy. Since it in no way cures or prevents these troublesome ulcers, four tablets a day for eight weeks would appear to be enough to help a patient during a particularly severe bout of ulceration. The resultant relief from pain may induce such a feeling of well-being that the ulceration may remain at a less severe level for a month or two, after which another period of therapy could then be tried if desired.

Summary

Assessment of the value of topical hydrocortisone hemisuccinate in the treatment of patients suffering from recurrent Mikulicz's aphthae has been undertaken by a double-blind controlled clinical trial. The results show that, compared with the placebo, the drug reduces by about 50% the number of ulcer days and of new ulcers per patient, per eight-weeks period.

Our thanks are due to Glaxo Laboratories Ltd. for providing the active and inert tablets, and to Guy's Hospital Medical Illustration Department for preparing the charts.

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BACTERIAL FLORA OF THE SMALL INTESTINE IN ACUTE INTESTINAL OBSTRUCTION

BY

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In acute obstruction of the small intestine the bowel above the site of obstruction soon becomes filled with fluid which is feculent, both in colour and in odour. When appropriate treatment is deferred, fluid of this nature may eventually be vomited.

It has usually been assumed that the flora of this fluid is closely akin to that of normal faeces. Moreover, it has generally been believed that the small intestine is inoculated with organisms by retrograde spread from the large bowel. A search of the literature of the past 60 years has not revealed any detailed investigation of the bacterial flora in intestinal obstruction in man.

In the work reported here, samples of intestinal content were taken at operation from many levels of the small bowel by aspiration of its content through hypodermic-needle punctures of the bowel wall. The specimens were then examined bacteriologically.

The results show that the small intestine above an obstruction contains a profuse flora of faecal type. This is abnormal. In contrast, the small intestine below the obstruction is either sterile or yields only a scanty growth. This is normal (Cregan and Hayward, 1953; Cook, Elliott, Elliot-Smith, Frisby, and Gardner, 1957). This leads to the conclusion that the profuse flora of faecal type present above an obstruction of the small intestine is acquired by ingestion.

Materials and Methods

Patients Studied.—Twenty-seven patients with intestinal obstruction were examined (Table I). Twenty-three obstructions were of the small intestine and were caused by herniae (9), bands or adhesions (10), obturation (2), volvulus (1), paralytic ileus (1). The bowel was considered to be gangrenous in two patients with strangulated herniae. The remaining four obstructions were in the large intestine, and were caused by diverticulitis (2) or carcinoma (2). The duration of the obstructions ranged from 6 hours to 10 days. No patient was accepted for study if any chemotherapy had been used.

Collection of Specimens.—Samples were taken in the following order: (*a*) stomach contents aspirated by

intragastric tube introduced before operation; (*b*) bacteriological swab of peritoneal fluid from the region of the obstructed bowel; (*c*) bacteriological swab of fluid from the hernial sac where appropriate; (*d*) bowel washing from the small intestine within 30 cm. below the point of obstruction, except when the obstruction was too near the ileo-caecal valve to allow such a specimen to be obtained; (*e*) bowel washing from within 30 cm. above the point of obstruction; (*f*) bowel washing from the first loop of jejunum distal to the duodeno-jejunal flexure; (*g*) bowel washing from the middle small bowel when the obstruction was in the terminal ileum or colon; and (*h*) bowel washing from the terminal ileum when the obstruction was in the colon.

All samples from the small intestine were taken during the emergency operation for relief of the obstruction. A gauge 21 needle was inserted obliquely through the bowel wall on its antimesenteric aspect while an assistant occluded the bowel lumen 3 cm. above and below the puncture, using either a clamp as illustrated (Fig. 1) or

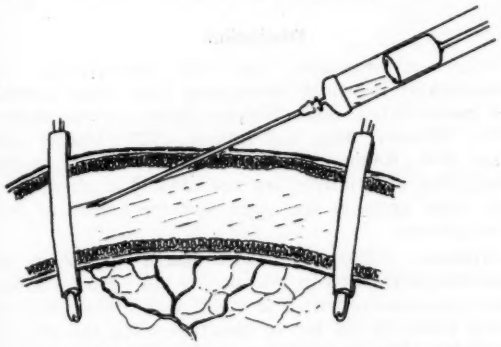

FIG. 1.—Method of sampling contents of small intestine.

preferably the more gentle grip of gloved fingers. Then 2 ml. of sterile Ringer's solution was instilled and washed to and fro from syringe to bowel lumen. The bowel washing was then withdrawn and examined bacteriologically.

Whenever possible the collapsed intestine below the site of obstruction was sampled before the obstructing factor was relieved. For this reason the band obstructions were approached by wide laparotomy incision, and the McEvedy (1950) technique was adopted for femoral herniae. Despite this, it was sometimes impossible to avoid partial relief of the obstruction during the early manipulations to determine its cause.

Bacteriological Examination

Immediately the collection of specimens was complete the following media were inoculated with the swab or with 2 drops (0.06 ml.) of the bowel washings or gastric aspirate: horse-blood agar and plain desoxycholate agar, incubated aerobically at 37° C.; horse-blood agar incubated anaerobically at 37° C. with 5–10% carbon dioxide.

The method of inoculation and interpretation of results on a quantitative basis was the same as that described by Cregan and Hayward (1953). The amount of growth was graded as follows: +/− or +, a scanty flora, normal in the small intestine and stomach; ++ and +++, a profuse flora, abnormal at these two levels of the gastro-intestinal tract.

The plates were examined at intervals up to at least five days' incubation and all species isolated were identified as fully as possible. Staphylococci were classified according to the criteria of Shaw, Stitt, and Cowan (1951) and *Candida* species according to Martin, Jones, Yao, and Lee (1937). The systematic table recommended by Swift (1952) was used for streptococci, while *Bact. coli* and *Bact. aerogenes* were subdivided into types according to Wilson and Miles (1955). All other species were identified by reference to *Bergey's Manual* (Breed, Murray, and Smith, 1957). For convenience the species were classed as either oral or faecal types as shown in Table II.

Direct smears of all specimens were made and examined after staining by Gram's method. These observations were correlated with the results of culture, and provided a check on the adequacy of the range of media and conditions of incubation used.

TABLE I.—*Gastro-intestinal Flora in Intestinal Obstruction*

Case No.	Level	Duration	Cause	Quantitative Results						
				Stomach	Jejunum	Mid-gut		Ileum		Colon
						Above	Below	Above	Below	
1	Mid-gut	1 day	Hernia	—	+++F	+++F	±F			
2	,,	1 ,,	,,		++O+++F	+++F	+F			
3	,,	2 days	,,		++F	++O+++F	—			
4	,,	3 ,,	,,		+++O++F	++F	±F			
5	,,	3 ,,	Adhesion		++F	+++F	±F			
6	,,	3 ,,	Volvulus		+++F	+++F	±F			
7	,,	4 ,,	Hernia		++++O+++F	++O+++F	—			
8	,,	4 ,,	,,	++F	++F	++F	±F			
9	,,	7 ,,	Adhesion	+++F	+++F	+++F	+++F			
10	Ileum	6–12 hours	,,		—	+++F				
11	,,	12 ,,	,,		+O+F			+O+F	—	
12	,,	12 ,,	Hernia		±O	+O+++F		+O+++F	±F	
13	,,	1 day	Adhesion		—			++F	++F	
14	,,	2 days	Obturation	++F	++O++F			+++F	—	
15	,,	3 ,,	Adhesion		+++F	+++F		+++F	+++F	
16	,,	4 ,,	Hernia		++O+++F			++O+++F	—	
17	,,	4 ,,	,,					+++F	—	
18	Terminal ileum	2 ,,	Adhesion		—			+++F		
19	,,	3 ,,	,,	++F	+++F	+++F		+++F		
20	,,	3 ,,	Obturation		+++F	+++F		+++F		
21	,,	4 ,,	Adhesion	+++O+++F				++O+++F		
22	,,	10 ,,	,,	++O++F	++O++F			++O++F		
23	,,	2 ,,	Ileus		+++F	+++F		+++F		
24	Colon	1 day	Diverticulitis		+O	+O		±O+F		+++F
25	,,	2 days	,,		+F	+++F		+++F		+++F
26	,,	7 ,,	Carcinoma		+++F	+O+++F		++F		
27	,,	14 ,,	,,		+++F	+++F		+++F		

The thick vertical lines denote level of obstruction. O indicates a flora of oral type and F indicates a flora of faecal type; ± to +++ indicate the degree of growth; — indicates no growth.

Results

Samples from Small Intestine Distal to the Point of Obstruction

Of the 16 samples taken 13 were either sterile (6) or contained a scanty flora (7). The remaining three (Cases 9, 13, and 15) yielded a profuse faecal flora which in each case was identical with the flora proximal to the obstruction. Two of these three cases were due to bands which were disturbed before the samples could be taken, and the other was regarded, at operation, as being incompletely obstructed. It was concluded that these three samples were mixed with material from above the point of obstruction and should be neglected in assessing the results.

The results, as set out in Table I, show that the small bowel contains only its normal scanty flora below any complete obstruction regardless of its level, of its duration, and of its cause.

Samples Proximal to the Point of Obstruction

Specimens from the small intestine immediately proximal to the point of obstruction contained a profuse faecal flora in 22 of the 23 cases of small-bowel obstruction and in three of the four cases of large-bowel obstruction. Of seven patients in whom obstruction had been present for less than 24 hours (Cases 1, 2, 10, 11, 12, 13, and 24) six yielded only a scanty growth from the stomach or jejunum. In contrast, of the 17 patients in whom the obstruction had been present for more than one day, only two (Cases 18 and 25) yielded a scanty flora in the proximal small intestine. It seems clear from these observations that, given time, an abnormal profuse flora of faecal type develops in the small intestine above any obstruction, regardless of its level or its cause.

It was observed that there was a correlation between distension of the small intestine and the presence of an abnormal flora. A profuse faecal flora was obtained from all 18 samples taken from distended bowel, whereas all five samples taken from bowel which appeared normal at operation yielded either sterile (2) or scanty (3) cultures. The six gastric samples which grew faecal flora were turbid and frankly feculent.

A list of the bacterial species and the number of occasions on which each was found in specimens of small-intestine and stomach contents that were quantitatively abnormal (++ or +++ growth) is given in Table II. Species of faecal type predominate, but oral-type organisms were occasionally isolated.

TABLE II.—*Nature of Abnormal Flora in Small Intestine in Intestinal Obstruction*

Species of Faecal Type	No. of Isolations	Species of Oral Type	No. of Isolations
Bact. coli type 1	22	*Str. mitis*	9
Cl. welchii	22	*Str. MG*	6
Paracolon sp.	18	*Staph. saphrophyticus*	3
Bacteroides sp.	14	*H. parainfluenzae*	2
Str. faecalis	11	*Str. salivarius*	2
Proteus mirabilis	9	*N. sicca*	1
Bact. aerogenes type 1	5	*Str.* group C	1
Bact. coli intermediate type	3	*Lactobacillus* sp.	1
Cl. multifermentans	3	*H. aphrophilus*	1
Veillonella parvula	3	*C. xerosis*	1
Candida albicans	3		
Cl. tetanomorphum	2		
Anaerobic streptococcus	2		
Bact. coli irregular type	2		
Cl. tertium	1		
,, *bifermentans*	1		
,, *capi ovale*	1		
,, *cochlearium*	1		
Achromobacter butyri	1		
Alcaligenes faecalis	1		

Number of patients with a profuse (abnormal) flora = 25.

Coliforms were isolated from all of the 25 patients who showed an abnormal flora, and generally outnumbered other species present. Usually two or more "coliform" species were isolated from each patient, *Bact. coli* type 1 being found most frequently. *Clostridium welchii* was present in 22 patients, but in 10 of these in relatively small numbers. *Bacteroides* species were present in 14 patients, an incidence which is less than in normal faeces (Eggerth and Gagnon, 1933).

Peritoneal and Hernial-sac Swabs

Peritoneal swabs (13) and hernial-sac swabs (6) were always sterile when the bowel was viable. In two patients with strangulated femoral herniae of four days' duration the bowel was found at operation to be gangrenous. In one of these patients both peritoneal and hernial-sac swabs were sterile. In the other patient the peritoneal swab was sterile but the hernial sac yielded a pure culture of *Proteus mirabilis*, though a mixed faecal flora (*Proteus mirabilis, Bact. coli* intermediate type 1, *Cl. welchii, Cl. multifermentans*) was present in the lumen of the herniated bowel.

Discussion

Many investigations into the bacteriology of experimental intestinal obstruction have been carried out, particularly in dogs (Whipple, Stone, and Bernheim, 1913; Meleney, Berg, and Jobling, 1927; Harper and Blain, 1945; Rabinovici and Fine, 1952). Though results from these experiments are not directly applicable to man, they agree in the main with the results of this investigation.

Williams (1926, 1927) investigated the flora in intestinal obstruction in man during life. However, his specimens were restricted to vomitus or swabs from the bowel lumen at the site of resection when this proved necessary. His bacteriological techniques were directed to the isolation of *Cl. welchii*, and little interest was taken in the many other organisms present. Williams also reported on the flora of the small bowel at necropsy in patients who had died of intestinal obstruction or peritonitis. However, the results tabulated by Blacklock, Guthrie, and Macpherson (1937) show that post-mortem bacteriological studies do not reliably reflect the situation before death.

The direct sampling technique used in the present investigation has yielded a clear picture of the flora in the lumen of the stomach and small intestine in the presence of obstruction. Bacteriological techniques used have allowed the isolation and full identification of all micro-organisms present within the bowel lumen.

The results of this investigation presented two different pictures, which are illustrated in Figs. 2 and 3. These are diagrams of two typical simple obstructions (Cases 12 and 14). In Fig. 2 the obstruction had been established for 12 hours, and in Fig. 3 for 48 hours. It will be seen that both distension of the small bowel and the presence of a profuse faecal flora above the obstruction extend proximally with the passage of time, whereas the small bowel below the obstruction contains only a scanty flora irrespective of the duration of obstruction. Though the diagrams represent obstructions in the ileum, no difference in bacterial flora was found in obstructions at other levels. Similarly, the nature of the obstructing agent did not affect the bacteriological picture.

These findings fail to support the belief that the profuse faecal flora in the small bowel and stomach proximal to an obstruction is derived directly from the

colon (Penman and Pullan, 1958). Instead the abnormal flora must be derived from above, either from ingested foods and fluids or from the oro-nasopharynx. That this is so is shown clearly by the findings (Fig. 4) in one hernial obstruction (Case 16). The faecal type of flora proximal to the obstruction could not have been derived from the distal bowel because of the zone of oral type bacteria present within the herniated loop. If faecal bacteria had passed through this segment by retrograde spread they would rapidly have overgrown the less robust oral type of bacteria in the herniated loop.

Since the profuse faecal flora present above an intestinal obstruction is derived from ingestion, the species of micro-organisms found in this study must be continually contaminating the healthy small intestine. However, the healthy small intestine contains so few micro-organisms that the species present have been regarded as only transient contaminants (Cregan and Hayward, 1953). Thus the healthy small bowel must possess the ability to prevent the establishment of these species as a resident flora. This ability is independent of the gastric germicidal barrier (Cregan, Dunlop, and Hayward, 1953). The nature of the mechanisms involved in preventing the establishment of a resident flora in the small intestine is not fully understood. However, it is clear that arrest of onward passage of bowel contents alters conditions in the small intestine above the point of obstruction so radically that organisms of faecal type proliferate rapidly. These findings have practical significance.

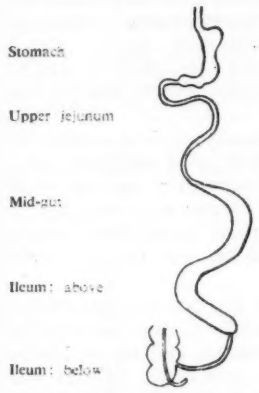

FIG. 2.—Case 12. Typical early ileal obstruction (12 hours).

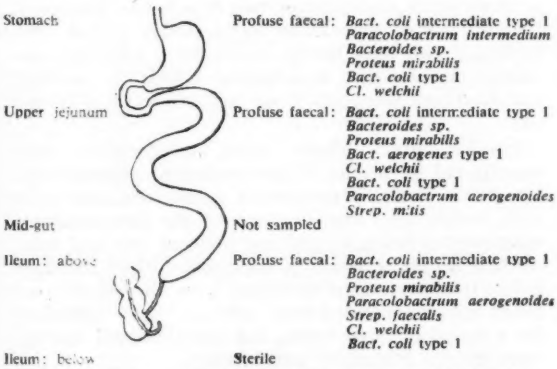

FIG. 3.—Case 14. Typical late ileal obstruction (48 hours).

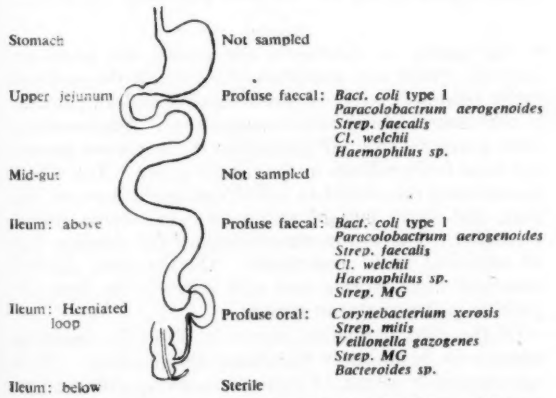

FIG. 4.—Case 16. Late obstruction with herniated loop of ileum.

Infective complications are common after surgery for intestinal obstruction. They range from minor wound infection to peritonitis with subphrenic or pelvic abscess and even to septicaemia. The bacterial flora of secondary peritonitis (Gillespie and Guy, 1956) and of a high proportion of wound infections after gastro-intestinal surgery (Ralston and Cowling, 1959) resembles that of the contents of the small intestine proximal to an obstruction. Hence any soiling of the peritoneum or wound with these contents is dangerous. In addition to an immaculate aseptic surgical technique, the parenteral administration of a suitable antibiotic pre-operatively should help by saturating the tissues of the host so as to protect them in the event of accidental soiling. It is recommended that immediately before operation either 250 mg. of tetracycline should be given intravenously in a saline infusion or alternately 1 mega unit of penicillin and 0.5 g. of streptomycin should be given intramuscularly. These doses should be repeated six-hourly post-operatively.

Summary

The bacteriology of the content of the small intestine in intestinal obstruction has been investigated. Samples were taken from the bowel at many levels, both above and below the obstruction. A profuse flora, predominantly of faecal type, was demonstrated above the point of obstruction. The longer the duration of the obstruction the further proximally did this flora extend.

The small bowel below the site of complete obstruction was sterile or contained only a scanty transient flora.

It is postulated that the infection in the lumen of the bowel above an obstruction is derived from ingested food and fluids or oro-nasopharyngeal secretions and not from a retrograde spread from the colon as has been thought hitherto.

We thank Dr. Nancy Hayward for constant help and advice, especially to one of us (R. F. B.), Professor S. D. Rubbo for helpful criticism, and the surgical staffs of the Alfred and Royal Melbourne Hospitals for their co-operation.

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TREATMENT OF TRICHURIASIS WITH DITHIAZANINE IN A HOSPITAL FOR MENTAL DEFECTIVES

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Since the publication of our preliminary report (Paine *et al.*, 1959) on the treatment of six patients known to be infected with trichuriasis, it has been possible to plan a controlled trial experiment with dithiazanine and arrange a full-scale treatment programme of all whipworm carriers at Coldharbour Hospital.

While the preliminary trial appeared to provide evidence of the efficacy of dithiazanine against human trichuriasis, the number of patients treated was small, and it was thought that the results might have been influenced by previous trials with other anthelmintics. Moreover, no control group of patients had been studied and there had been no long-term follow-up examinations to determine the possibility of relapse or reinfection.

Controlled Trial

Method

Twenty-four patients known to be infected with whipworm were chosen, 12 being selected for treatment with dithiazanine and 12 to serve as controls. Some attempt was made to match the individual patients for treatment and control in respect of their pre-treatment egg counts, and it was possible to allocate an approximately equal number with light and medium infections to each group. No claim is made, however, that a patient's whipworm load can be estimated from his faecal egg count.

The treatment group received dithiazanine orally, as "telmid" tablets, in the same dose as that used in the preliminary trial—that is, 200 mg. three times a day for five days, regardless of age and weight. The patients' weights in this trial ranged from 60 to 151 lb. (27 to 68.5 kg.). In view of the possible association between vomiting and failed treatment in the preliminary trial, the five-day course of dithiazanine was extended on this occasion by one additional 200-mg. dose of the drug for every dose interval when vomiting occurred. A tendency to constipation had been noted in the previous trial, and patients in both treatment and control groups therefore received two "senokot" tablets on each of the five treatment days, followed by two tablets three times weekly for the next two weeks.

Pre-treatment egg counts were carried out by the Stoll (1947) technique, since this method gives some indication of the severity of the whipworm infestation. Ten days after the completion of treatment, further faecal examinations were made by De Rivas's (1928) concentration technique, giving either positive or negative results only.

From the first day of treatment, a careful search was made for the adult whipworm, all faecal specimens being examined for 10 days, and, thereafter, one specimen weekly for three weeks. The worms were immediately placed in distilled water at room temperature, where they remained for 24 hours so that any motility might be noted.

All patients were observed for possible side-effects, and ward records were kept of the four-hourly temperatures, daily blood-pressures, and the incidence of vomiting and diarrhoea in each case. Pyrexia was taken to mean an axillary temperature of at least 99° F. (37.2° C.), and temperatures were recorded over a period of three weeks, commencing two days before treatment. Blood-pressures were taken for a 10-day period, also beginning two days before treatment. Vomiting was charted once for each dose interval in which it occurred, and diarrhoea when two loose motions occurred in one day.

Possible toxic effects from dithiazanine were investigated by means of haematological examinations, blood-urea levels, serum-protein estimations, and urine tests, before and after treatment; the post-treatment examinations being carried out between one and three weeks after the cessation of treatment. From two days before treatment, urine specimens from all patients were tested daily on the ward with "albustix" and "clinistix" for a period of three weeks, and any abnormal findings were sent for laboratory confirmation.

None of the patients selected had received anthelmintics during the two years preceding this trial.

Results

The results of the faecal egg counts are given in Table I. With one exception (Case 4), all the patients under treatment were rendered negative and all patients in the control group remained positive. Adult worms were recovered from all patients in the treatment group, but none from patients in the control group. The whipworms were discovered in faecal specimens between the third and sixth days of treatment, none being found thereafter. The worms were examined for motility, but all appeared to be non-viable. On the third day of treatment threadworms were seen in specimens from six patients in the treatment group.

Of the clinical findings shown in Table II, vomiting appears to be the only significant complication. This occurred in 7 of the 12 patients receiving dithiazanine but not at all in the controls. An analysis of the days

on which vomiting occurred shows that four of the seven patients vomited on the first day, four on the second day, two on the third day, one on the fourth day, two on the fifth day, and one on the sixth day of treatment. There was thus a tendency for patients to vomit more on the first and second treatment days, but one patient vomited a second time on the sixth day, and another on the fifth day only. Pyrexia did not occur except in Case 7 of the control group. This patient showed a transient rise of temperature before an epileptic convulsion. Diarrhoea was general, and this may be related to the routine administration of senokot tablets as described above; and the transient lowering of systolic and diastolic blood-pressures in a number of cases may also be attributed to the same symptom.

TABLE I.—*Results of Treating Trichuriasis with Dithiazanine, Showing the Egg Carrier State Before and After Treatment and the Number of Adult Worms Recovered. Comparative Findings are Given for Untreated Controls*

Case No.	Pre-treatment Egg Counts. Average per Gramme of Faeces. Stoll Technique	Post-treatment Examination of Faeces for Trichuris Eggs. De Rivas's Concentration Technique	No. of Adult Trichuris in Stools	Threadworms Present in Stools
Treatment Group				
1	100	—	46	—
2	200	—	6	Present
3	600	—	11	—
4	900	Present	12	Present
5	3,200	—	10	—
6	3,600	—	18	Present
7	4,900	—	7	—
8	5,200	—	23	Present
9	5,400	—	131	,,
10	6,800	—	121	—
11	7,400	—	35	Present
12	9,200	—	92	—
Control Group				
1	<100	Present	—	—
2	100	,,	—	—
3	500	,,	—	—
4	500	,,	—	—
5	700	,,	—	—
6	1,400	,,	—	—
7	1,400	,,	—	—
8	1,400	,,	—	—
9	1,500	,,	—	—
10	2,000	,,	—	—
11	4,700	,,	—	—
12	5,800	,,	—	—

TABLE II.—*Clinical Side-effects of Treating Trichuriasis With Dithiazanine, Showing the Incidence of Pyrexia, Fall of Blood-pressure, Vomiting, and Diarrhoea in Treatment and Control Groups*

Case No.	No. of Days When Pyrexia Occurred	Treatment Days When Systolic and Diastolic Blood-pressures Fell by 10 mm.	No. of Dose-intervals When Vomiting Occurred	No. of Days When Diarrhoea Occurred
Treatment Group				
1	—	—	2	5
2	—	—	1	1
3	—	2nd	6	6
4	—	5th	—	1
5	—	—	1	4
6	—	2nd, 4th, 9th	1	2
7	—	—	—	1
8	—	1st, 6th	—	4
9	—	2nd	—	3
10	—	6th	12	1
11	—	—	—	2
12	—	2nd, 4th	2	2
Control Group				
1	—	2nd, 8th	—	4
2	—	1st	—	2
3	—	—	—	1
4	—	6th	—	2
5	—	9th	—	5
6	—	—	—	3
7	1	—	—	1
8	—	6th	—	1
9	—	—	—	3
10	—	1st	—	1
11	—	—	—	2
12	—	—	—	4

The results of the laboratory examinations, shown in Tables III and IV, provide no evidence of toxicity. The

TABLE III.—*Results of Haematological Examinations Before and After Treating Trichuriasis With Dithiazanine. Findings are Given for Treatment and Control Groups*

Case No.	Pre-treatment Examinations: Hb (%)	Pre-treatment Examinations: Total White Cells	Pre-treatment Examinations: Description	Post-treatment Examinations: Hb (%)	Post-treatment Examinations: Total White Cells	Post-treatment Examinations: Description
Treatment Group						
1	87	4,900	Normal	99	8,500	Normal
2	90	9,600	6% eosinophils. Otherwise normal	108	9,000	,,
3	81	7,600	Normal	91	6,000	,,
4	84	8,200	,,	92	7,000	,,
5	73	7,000	,,	100	6,400	,,
6	84	5,000	,,	94	4,600	,,
7	84	9,700	10% eosinophils. Otherwise normal	81	7,600	7% eosinophils. Otherwise normal
8	92	6,800	Normal	110	5,600	Normal
9	81	8,200	,,	78	6,800	,,
10	78	10,000	6% eosinophils. R.B.C.s hypochromic and microcytic	81	8,400	,,
11	87	7,100	Normal	103	11,000	,,
12	87	8,600	,,	85	9,000	,,
Control Group						
1	95	10,600	Normal	89	8,600	Normal
2	84	7,400	,,	114	9,900	,,
3	78	5,200	R.B.C.s hypochromic. Differential white cells normal	87	6,800	,,
4	80	9,700	Normal	87	10,400	,,
5	90	6,100	,,	86	8,400	,,
6	64	6,400	R.B.C.s microcytic. Differential white cells normal	92	10,200	,,
7	76	9,000	Normal	83	7,200	,,
8	87	8,200	,,	91	6,000	,,
9	78	7,600	7% eosinophils. Otherwise normal	77	6,600	,,
10	95	5,600	Normal	95	8,200	,,
11	95	5,400	,,	73	7,000	,,
12	87	8,300	No film	84	11,600	,,

TABLE IV.—*Results of Blood Urea, Serum Protein, and Urine Examinations Before and After Treating Trichuriasis With Dithiazanine. Findings are Given for Treatment and Control Groups*

Case No.	Pre-treatment Examinations: Blood Urea (mg./100 ml.)	Pre-treatment Examinations: Serum Protein (g./100 ml.)	Pre-treatment Examinations: Urine	Post-treatment Examinations: Blood Urea (mg./100 ml.)	Post-treatment Examinations: Serum Protein (g./100 ml.)	Post-treatment Examinations: Urine
Treatment Group						
1	30	5·4	—	49	6·7	—
2	44	6·1	Trace albumin and sugar	48	6·5	Trace albumin
3	31	6·8	—	48	6·4	—
4	51	6·8	—	52	7·0	—
5	33	6·0	—	37	6·5	—
6	45	6·8	—	37	6·5	—
7	31	7·0	—	37	6·8	—
8	21	6·1	—	43	6·7	—
9	51	6·7	—	46	7·0	—
10	40	6·7	Trace albumin and sugar	37	6·5	Trace albumin
11	36	7·2	—	45	7·2	—
12	24	5·5	Trace albumin	32	6·5	Trace albumin
Control Group						
1	41	7·2	—	42	7·2	—
2	51	7·2	—	52	6·8	—
3	48	5·4	—	46	6·1	—
4	48	6·5	—	35	6·5	Albumin, epithelial cells, scanty R.B.C.s
5	36	6·1	Trace albumin	40	6·3	Trace albumin, occasional polymorph
6	32	6·8	—	38	6·5	—
7	32	7·3	—	36	6·7	—
8	25	7·2	—	40	6·7	—
9	52	6·5	—	43	6·5	—
10	30	7·2	—	36	6·8	—
11	35	7·4	—	40	7·2	—
12	31	6·8	—	48	6·3	—

figures for haemoglobin and total white cells (Table III) and for blood urea and serum protein (Table IV) were within normal limits before and after treatment. Abnormalities in the urine (Table IV) occurred in certain patients from the treatment group, but also in some of the controls, and, in any event, these proved to be transient changes possibly associated with an intercurrent infection in the ward.

Conclusions

The controlled trial experiment confirms the impression gained from our preliminary trial that dithiazanine iodide, given as an oral dose of 200 mg. three times daily for five days, is an effective anthelmintic against human trichuriasis. Not only is the faecal egg count reduced to zero in a high proportion of cases, but it seems that adult worms also are eliminated by the sixth day of treatment.

The use of a laxative concurrently with dithiazanine in this trial did not significantly alter the rate of egg clearance observed in the preliminary trial (11 of 12 patients cleared of eggs as against five of six in the preliminary trial). Since the combined use of dithiazanine and a laxative failed to achieve total egg clearance, other methods of treatment should be considered.

In agreement with the findings of Swartzwelder *et al.* (1957), no worms recovered from treated patients showed motility after immersion in distilled water; but, since further experiments with nutrient media were not carried out, no evidence was obtained as to viability.

Apart from the occurrence of vomiting in more than half of the patients treated, the trial shows an apparent absence of clinical side-effects in mental defectives (see below). A tendency for vomiting to occur during the first two days of treatment is noted.

From the results of haematological examinations, blood-urea levels, serum-protein estimations, and urine tests, dithiazanine appears to be non-toxic in the dosage used in this trial.

Mass Treatment Programme

At the close of the controlled trial experiment it was decided to extend the treatment programme to cover all possible whipworm carriers in the hospital. While trichuris eggs are sometimes found in faecal specimens from the general population, and while a hospital population may be open to reinfection from outside sources, it seemed reasonable to plan a full-scale treatment programme with dithiazanine if concurrent disinfection of the hospital buildings and grounds were arranged. Any risk of subsequent reinfection from outside sources would be covered by routine egg counts from new admissions and other possible contacts.

Preparation for Mass Treatment

Of the 154 patients resident, only 81 were known to be whipworm carriers; but it was decided to treat all patients simultaneously, so that any who might have been whipworm carriers despite a negative faecal egg count should also be freed from the infestation. The hospital staff had not been examined previously for whipworm, but shortly before the mass treatment of patients was due to begin selected members of the staff, known to have been in contact with infected patients, were asked to submit specimens of faeces. From the first 12 members of the staff examined, one was found to be whipworm-positive; and two more positive results were reported from a further group of specimens. All staff working at the hospital were then asked to take part in a mass treatment programme, and each of the small minority who declined sent three specimens for testing; all were shown to be whipworm-negative. Three staff dogs were tested for whipworm, but were all reported negative. Though it is known that the human and canine forms of whipworm are distinct species, the dogs were examined to extend the search for possible carriers.

The destruction and removal of trichuris ova from the hospital estate and buildings presented a major problem. As moisture is favourable to embryonation, the various methods of disinfection which depend on antiseptic solutions were regarded as unsuitable. Samples of soil from the hospital estate had failed to show the presence of trichuris ova, but it was decided to burn with flame guns all hospital roadways and areas of grass that had been liable to contamination by patients. The wards, and the hospital buildings where whipworm carriers had been accommodated, were to be cleaned systematically with vacuum cleaners, and any ward floors and other surfaces that had been wax-polished would be cleaned with turpentine 24 hours beforehand. All the patients' furniture, bedding, clothes, books, and small equipment would be cleaned by vacuum, and selected items would be sterilized by autoclave also. The disposable paper containers and filters from the vacuum cleaners would be destroyed daily in the hospital incinerator.

Four empty wards, considered free from trichuris ova, would be made ready to accommodate the patients while their regular wards were being cleaned.

Method

Several days before the mass treatment was due to begin, all staff had been issued with a five-day course of dithiazanine tablets, to be taken as from the first treatment day. Staff on leave during the mass treatment were advised to complete the course before returning to duty.

Also before treatment, vacuum-cleaning had been started in a small annexe of single rooms to be made available for a group of patients specially selected for kitchen duties during the treatment programme.

On the first treatment day all patients were confined to their wards to receive a five-day course of dithiazanine tablets. The same dosage was used as in the control trial, and, on this occasion also, treatment was continued by one additional 200-mg. dose of dithiazanine for every dose interval when vomiting occurred. Records of vomiting and observations regarding general health were kept in the ward, but in view of the results of our controlled trial experiment other possible side-effects were not specially considered. Two weeks after cessation of treatment every patient's urine was tested with albustix and clinistix and any abnormalities were sent for laboratory confirmation (see below).

On the fifth day of treatment arrangements were made to transport all the patients to temporary accommodation. The selected kitchen workers were taken to the small annexe already described, and the remaining patients removed to the empty wards prepared for them. The flaming of the hospital roadways was carried out in sections to provide, at an early stage, "clean" routes between the regular wards, the kitchen unit, and the temporary accommodation. Kitchen dustbins were also flamed at this time.

Before leaving his regular ward each patient was bathed. He was then wrapped in a clean blanket and conveyed by wheel-chair to his temporary abode. On being received into this unit he was provided with a cleaned and vacuumed set of clothes by the nurses awaiting his arrival. Nursing staff entering the temporary wards left their shoes on the threshold and used a second pair for duty in the "clean" area.

All the patients continued in this temporary accommodation until their regular wards had been cleaned throughout, but after a 10-day absence the last patient was returned. By this time the main part of the hospital roadways had been flamed, and there was direct access to the wards and other departments. Many patients therefore returned to their usual occupations, and normal arrangements for holidays were resumed. Vacuum-cleaning of the occupational and recreational departments continued until three weeks after the patients had returned to their regular wards, and, on account of heavy rainfall, it was six weeks later before the contaminated areas of grass had been burnt with flame guns.

Post-treatment faecal examinations were made by De Rivas's (1928) concentration technique, with which even scanty ova will return a positive result. Specimens were sent to the laboratory from all patients and staff, including the small minority who had not accepted treatment; and, since more than 200 examinations were required, about 20 specimens were dispatched each week over a 10-weeks period. Any patient or staff returned positive received a further five-day course of dithiazanine tablets, and this was followed by the examination of further specimens of faeces. About three months after the mass-treatment programme had begun the situation was reviewed, and the immediate results of treatment were assessed. Six months after the mass treatment a second survey of faecal specimens was begun in order to obtain the long-term results of treatment. Intermediate examinations were made also in certain cases where relapse from treatment had occurred previously.

Reference has already been made to any side-effects observed in the patients during mass treatment. Members of the staff who had received dithiazanine were asked to describe their reactions. Their symptoms were then listed under vomiting, diarrhoea, constipation, malaise, headache, and "no complaints," and the main trends noted. It was appreciated, however, that there had been no control group amongst the staff, and that only tentative conclusions were possible.

Results—Patients

Three months after mass treatment started it was possible to make the first survey of results. 82 patients were known to have been positive at some time before mass treatment (18 of these had been treated with dithiazanine at a previous trial). Of the 64 whipworm carriers who had not received previous treatment, 54 (84%) became negative after one five-day course of dithiazanine. By including the patients treated at previous trials (since they had therefore received two courses of dithiazanine), it was found that 76 (93%) of the 82 whipworm carriers had become negative after two courses of treatment. Similarly, 81 (99%) of 82 became negative after three courses of treatment, the remaining patient requiring four courses before he became negative. At the time of the three-monthly review, therefore, all patients had become negative for whipworm as judged by the results of faecal examinations.

Nine months after mass treatment, when the results of the second survey were known, the long-term findings were assessed. Of the 82 patients originally positive for whipworm, nine had shown trichuris ova in faecal specimens examined since the three-monthly review. This represented a relapse of 11% from the immediate results of mass treatment. Further courses of dithiazanine tablets were given to the nine patients until they were all returned negative; four patients requiring one repeat course, four patients two, and one patient three repeat courses of treatment. The time interval between a patient's last negative specimen and his next positive specimen was noted in all relapsed cases, as this interval may be used in distinguishing between relapse from treatment and reinfection, by reference to the life-cycle of the whipworm. Since embryonation for three weeks outside the host and maturation for three months within the host are both needed to complete the egg-laying cycle, a "negative-to-positive" interval of less than 16 weeks would almost exclude the possibility of reinfection. Even when a fully embryonated egg enters the host immediately before treatment, a negative-to-positive interval of less than 13 weeks will still exclude reinfection. Some of the patients relapsed more than once, and there were in all 14 "negative-to-positive" intervals, eight of which were less and six more than 13 weeks. In considering these time intervals, however, allowance should be made for the delay arising from the long-term review of cases. All patients were reported negative for whipworm at the nine-monthly review, and further specimens two months later, from the relapsed cases, still gave negative results.

No attempt was made to count the adult worms in faecal specimens during the mass treatment, though many were observed.

Of the 154 patients receiving dithiazanine in the mass-treatment programme, 61 (40%) vomited. When the occasions of vomiting were analysed according to the treatment day, it was found that 40 occurred on the first day, 25 on the second, 25 on the third, 11 on the fourth, 27 on the fifth, 4 on the sixth, and 1 on the seventh day of treatment. As in the controlled trial experiment, there was a general tendency for patients to vomit in the early stages of treatment, but in a certain number of cases the reverse applied. No patient showed any other significant side-effects, and there was no diarrhoea.

When tested after mass treatment, 15 patients not included in the control trial showed traces of albumin and other minor abnormalities in the urine, but on further testing these changes proved to be transient and apparently unrelated to the administration of dithiazanine tablets.

None of the 82 patients originally found to be positive for whipworm had shown symptoms or signs attributable to the infestation, and after this treatment programme there was no obvious evidence of improved health in any of the patients receiving dithiazanine; but mental defectives do not readily complain of minor subjective symptoms.

Results—Staff

After the pre-treatment examination of specimens, two whipworm carriers were found who had been in contact with infected patients and one carrier who attended to the hospital drains. All three had been employed at the hospital for several years. Soon after the completion

of mass treatment, however, a new member of the staff was appointed who was found to be whipworm-positive. In this case there had been no previous connexion with the hospital, and the individual concerned lived several miles away in a small village. None of the staff responded to the first course of dithiazanine tablets, but one responded to the second course, another to the third course, and the third became whipworm-negative after four courses of treatment. The fourth member of the staff was given eight courses of dithiazanine tablets without effect, and as he was a regular consumer of alcohol (mainly cider), complete abstention was advised for one week, to be followed by a ninth course of treatment. This resulted in a series of negative faecal specimens without further relapse. The member of the staff who had required four courses of treatment returned a positive specimen at the nine-monthly review, but in this case one additional course of dithiazanine was followed by negative specimens.

Of the 56 staff who received dithiazanine tablets, 19 (34%) complained of vomiting, and in four cases this was severe enough to cause absence from work. 27 (49%) complained of diarrhoea and 21 (40%) had definite malaise. Less frequent were complaints of constipation (six cases) and headache (five cases). 27 members of the staff (49%) experienced a sense of general apathy which they associated with taking the tablets. 12 of the staff (23%) claimed that they were unaffected by the treatment.

Discussion

Swartzwelder *et al.* (1957) have demonstrated that satisfactory results are to be obtained from treating human trichuriasis with dithiazanine, and in our preliminary report (Paine *et al.*, 1959) we confirm these findings. Our controlled trial experiment and mass-treatment programme have been designed to discover whether patients with positive trichuris egg counts can be finally cleared from the infestation, and whether a partially closed community, such as a hospital for mental defectives, can be freed from whipworm by the use of dithiazanine.

The results described above provide evidence that about 80% of whipworm carriers show negative faecal specimens after one five-day course of treatment with dithiazanine. Failed cases may receive further treatment without apparent risk of toxicity. Our results have shown also that, while three courses of treatment produced negative faecal specimens in 99% of cases, a further review after six months may demonstrate return positives in 11% ; which will again respond, however, to further treatment with dithiazanine. The number of courses of treatment originally required to render a patient whipworm-negative has little influence on his tendency to relapse, since three of our relapsed cases first became negative after a single course of treatment and six after several treatments.

Relapse from treatment may be distinguished from reinfection by the negative-to-positive interval, which will exceed 13 weeks (or 16 weeks in most cases) if reinfection has occurred. These intervals are explained by the embryonation and maturation periods of the whipworm. On this basis the nine " return positives " at our long-term review were probably cases of relapse from treatment. Relapse would seem to imply that the whipworm has been protected in the body from the full effects of dithiazanine, and our case which failed to respond to treatment until alcohol was withheld suggests that this substance may enable the worm to withstand the effects of the dye.

Dithiazanine has been associated with vomiting in all our treatment trials, this occurring in 40% of patients and 34% of staff in the mass-treatment programme. Since there has been a general tendency for vomiting to occur early in treatment, some improvement might be expected if a smaller dose of dithiazanine were given during the first two days. In a proportion of cases, however, vomiting was increased on the fifth day of treatment, both in the controlled trial and in the mass-treatment of patients. Whether the response to treatment would be affected by a smaller initial dosage of dithiazanine is open to question, and, in this connexion, one should consider the risk of producing dithiazanine-resistant whipworms by undertreatment. We would prefer that vomiting should be minimized by the prophylactic use of one of the anti-emetic drugs now available.

It is of interest that the whipworm carriers at Coldharbour Hospital included one member of the staff who was found to be whipworm-positive without having had any previous connexion with the hospital or a history of travel abroad. One of us (T. V. C.), who has worked in this area for 20 years, has found that symptomless trichuriasis is endemic but comparatively uncommon.

No conclusions can be drawn regarding the effectiveness of the general measures to remove trichuris ova from the hospital buildings and grounds, since it was not possible to treat a control group without these precautions. To have provided such a control would have invalidated the treatment programme for the whole hospital, and, while we are without proof that these general measures were successful, there is no evidence that any case of reinfection occurred.

Summary

The treatment of trichuriasis with dithiazanine was studied in a hospital for mental defectives by means of a controlled trial with 24 patients, and this was followed by a mass-treatment programme which included 154 patients and 56 members of the staff. 80% of positive cases became whipworm-negative after one five-day course of dithiazanine, and after three such courses 99% showed negative faecal specimens.

Transient vomiting is the only side-effect of the treatment, and dithiazanine is without any demonstrable toxic effects.

The hospital was free from the infestation many months after the beginning of treatment.

We thank the nursing, artisan, and technical staff, who, by their unremitting efforts and co-operation, contributed so largely to the success of this treatment programme. We are grateful to Eli Lilly and Co. Ltd. for supplying " telmid " tablets and for a generous grant from their American Research Fund.

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SICKLE-CELL ANAEMIA COMPLICATED BY MEGALOBLASTIC ANAEMIA OF INFANCY

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The association between megaloblastic anaemia and various haemolytic anaemias is well documented. The most recent publications on the subject are by Chanarin *et al.* (1959) and Jonsson *et al.* (1959). The latter authors review 13 cases from the literature, and add three cases of their own. Two of these had sickle-cell anaemia, and the third sickle-cell/haemoglobin-C disease. These three cases are the first examples of such a combination in adults we could find in the literature.

The purpose of this communication is to report five cases of megaloblastic anaemia associated with sickle-cell anaemia. These five cases were found in a series of 50 cases of megaloblastic anaemia of infancy attributable to folic-acid deficiency (MacIver and Back, 1960). We have been able to find only one other report in the literature of this association in infancy (Zuelzer and Rutzky, 1953).

Methods

Standard haematological methods were used (Whitby and Britton, 1957). *In vitro* sickling tests were carried out, using 2% sodium metabisulphite (Daland and Castle, 1948). Filter-paper electrophoresis of haemoglobin was performed in a horizontal tank using barbitone buffer of *p*H 8.6 and ionic strength about 0.02 (Went and MacIver, 1956). Foetal haemoglobin was determined by the alkali denaturation technique described by Singer *et al.* (1951).

Bone-marrow aspiration was carried out using an Osgood (16 gauge) needle under local anaesthesia. The site of puncture selected was the upper end of the tibia about 2 in. (5 cm.) below the tibial tuberosity. The marrow films were stained by both Leishman's method and the May–Grünwald–Giemsa technique. A portion of the aspirated material was allowed to clot in the syringe, and the specimen so obtained was fixed and sectioned histologically as described by Mertens (1945). The sections were stained with haematoxylin and eosin, and for iron by the Prussian-blue technique of Perls. All the sections were stained for iron simultaneously to minimize technical errors.

The relevant haematological findings are given in the Table.

Pertinent Haematological Data

Case No.	Sex	On Admission					Maximum Reticulocyte Response (%)	Days After Beginning of Folic-acid Therapy	On Discharge		
		Age (Months)	Hb (g./100 ml.)	Reticulocytes (%)	W.B.C.	Nucleated Red Cells/100 W.B.C.			Hb (g./100 ml.)	Reticulocytes (%)	Foetal Hb (%)
1	M	12	2·8	1	24,000	63	50	15	6·6	30	0–5½
2	M	14	3·2	12	12,000	164	30	3	6·5	10	14½
3	M	12	3·6	5	22,000	57	46	4	6·0	28	10
4	F	10	4·1	11	4,000	469	32	7	8·0	32	16
5	F	13	3·2	5	18,000	6	58	6	9·0	30	9½
Mean		12	3·4	7	16,000		43	7	7·2	26	11

Case 1

A male infant, aged 1 year on his first admission to hospital, had developed fever and yellow eyes at the age of 6 months, and the jaundice had been present ever since. He suffered from attacks of fever every two or so weeks. He was breast-fed for eight months, and then weaned on to "quaker" oats and condensed milk, with "ovaltine" at night and one egg a week.

On examination he was very anaemic and slightly jaundiced. His nutritional state was poor — weight 13 lb. 14 oz. (6.3 kg.). The hair was sparse, wiry, and reddish in colour. The liver and spleen could not be felt, but a few small, shotty, mobile glands were palpable in all areas. There was minimal oedema of the feet. The *in vitro* sickling test was positive. A diagnosis of sickle-cell anaemia was made. As his general condition was fair he was observed for a few days and treated with intramuscular iron. After blood transfusions he was discharged with a haemoglobin level of 12.4 g./100 ml.

Fifty-five days later he was readmitted with a story that he had remained well until three weeks previously, when he developed a chest cold and fever. A week before admission he began vomiting after his feeds, but he had no diarrhoea.

On examination the child was miserable and cried constantly. His nutritional state was poor (weight 11 lb. 8 oz.—5.2 kg.), and he was obviously anaemic. The hair was dry, reddish in colour, and sparse. There was no oedema. The haemoglobin level was 6.3 g./100 ml., the white-cell count 2,600/c.mm., the reticulocyte count 0.4%, and, surprisingly, in view of the previous diagnosis of sickle-cell anaemia, haemoglobin electrophoresis revealed

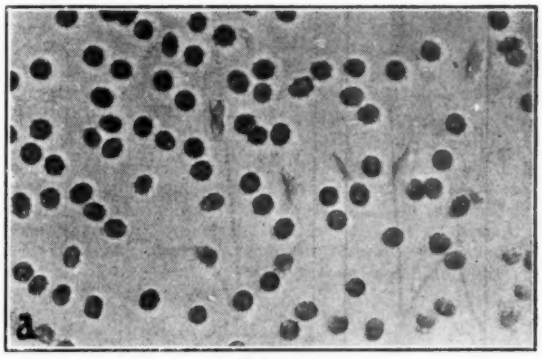

FIG. 1A

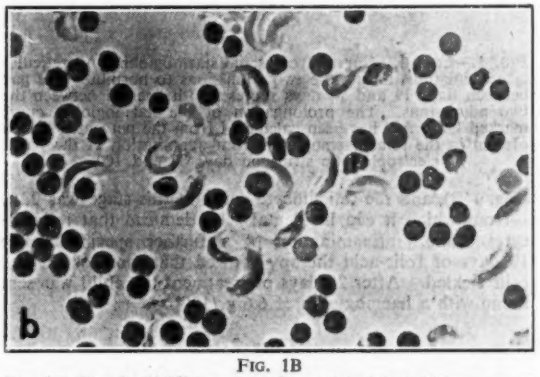

FIG. 1B

FIG. 1.—Case 1. Sickling preparations of the blood (A) on second admission, (B) six days after the beginning of folic-acid therapy.

haemoglobin type A only, and the *in vitro* sickle-cell test was negative. A closer examination of the sickle preparation showed, however, that about 1% of the red cells were in fact sickling (Fig. 1 A). As there was no reason to doubt the original diagnosis of sickle-cell anaemia (though haemoglobin electrophoresis had not been performed during the previous admission) it was thought that folic-acid deficiency was likely and that his red cells consisted largely of those transfused on the earlier admission. The bone-marrow was therefore examined, and found to be megaloblastic (Fig. 2). Treatment with folic acid (10 mg. per day) was instituted and a striking reticulocytosis resulted which reached a maximum of 50% 15 days after beginning treatment (Fig. 3). A repeat sickling test after six days of folic acid showed that about 20% of the cells sickled (Fig. 1 B), and the reticulocyte count at this stage was 22% —from which it can incidentally be deduced that reticulocytes sickle. Examination of a further specimen after 19 days of folic-acid therapy showed that most of the red cells sickled. After 28 days of treatment the child was sent home with a haemoglobin of 6.6 g./100 ml.

FIG. 2.—Case 1. Bone-marrow before the beginning of folic-acid therapy on second admission, showing changes in the granulocytes characteristic of megaloblastic anaemia.

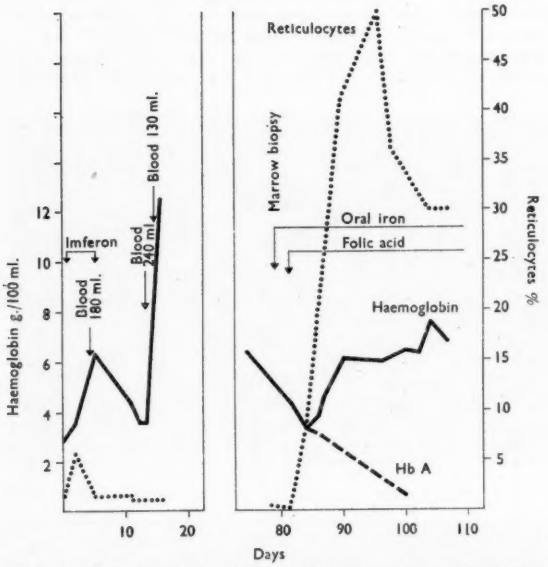

FIG. 3.—Case 1. Curves from serial haemoglobin and reticulocyte estimations during the two admissions to hospital. The gap between days 19 and 74 days represents the period between the two admissions. The prolongation of the haemoglobin curve marked "Hb A" has been calculated from the percentage Hb S present in the total haemoglobin from quantitation of the paper electrophoretic strips on days 87 and 100.

Case 2

A male infant aged 14 months was admitted to hospital because of loss of appetite and progressive pallor during the preceding month He had been breast-fed for eight months and then weaned on to "ostermilk" and "milo" sweetened with condensed milk. He also received soup, fish tea, Irish potatoes, bread, biscuit, and egg-white every other day. He was well until a month before admission, when he began refusing his feeds, and then lost weight. His mother noticed that his skin was becoming increasingly pale, and he developed a cold and cough with fever especially at night. His condition had deteriorated rapidly during the preceding week. At no time had he had diarrhoea or vomiting, and there was no history of jaundice.

On examination he was an extremely pale child of fair nutritional state—weight 17 lb. 7 oz. (7.9 kg.). The temperature was 101° F. (38.3° C.). There was no jaundice. Some frontal bossing of the skull was seen, and the hair was sparse. The skin was normal, and there was no oedema. A generalized slight lymphadenopathy was present, the liver was palpable 1½ in. (4 cm.) below the costal margin, and the spleen was also enlarged, being felt 1 in. (2.5 cm.) below the costal margin. The chest was clear.

Haemoglobin electrophoresis showed type S haemoglobin only. Bone-marrow biopsy revealed a frankly megaloblastic pattern (Fig. 4). A diagnosis of sickle-cell anaemia complicated by megaloblastic anaemia was made. A smear of peripheral blood was found to contain megaloblasts (Fig. 5).

Treatment with folic acid (10 mg. per day) was begun, and three days later the reticulocyte count had risen from an initial value of 12% to 30%. Ten days after the start of folic-acid therapy the haemoglobin level had risen to 6.7 g./100 ml., and when the child was seen on follow-up

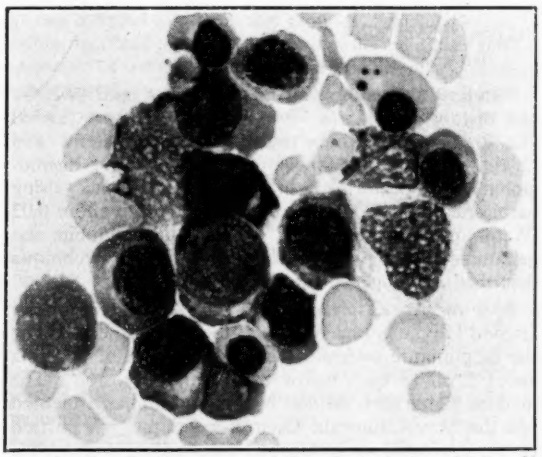

FIG. 4.—Case 2. Bone-marrow before the beginning of folic-acid therapy, showing megaloblastic erythropoiesis.

FIG. 5.—Case 2. Peripheral blood smear before the beginning of folic-acid therapy, showing megaloblasts.

a month later the haemoglobin level was 8.5 g./100 ml. and the reticulocyte count 13%.

Case 3

A male infant aged 1 year was admitted to hospital because of refusing feeds for three weeks and increasing pallor for one week. He had been breast-fed for six months, and was then weaned on to condensed milk and cornmeal porridge. Occasionally he was given cow's milk instead of condensed milk if any was available. He was apparently quite well until three weeks before admission, when he started to refuse feeds. Thereafter he deteriorated rapidly, losing weight and becoming increasingly pale. He had been feverish day and night for a week, but had no cold or cough. There was no history of vomiting or diarrhoea, and no history of jaundice.

On examination the child looked ill and extremely pale. The temperature was 101° F. (38.3° C.). His nutritional state was good—weight 19 lb. 4 oz. (8.7 kg.)—he was not dehydrated, and jaundice was absent. The lymphatic nodes were slightly enlarged in all areas. There were no skin or hair changes, but a trace of ankle oedema was observed. The liver was palpable 1½ in. (4 cm.) and the spleen ½ in. (1.3 cm.) below the costal margin. Haemoglobin electrophoresis showed type S haemoglobin only. Bone-marrow biopsy disclosed a strikingly megaloblastic pattern. A diagnosis of sickle-cell anaemia complicated by megaloblastic anaemia was made.

Treatment consisted of skimmed milk and mixed feeding, which he took well from the outset, and oral folic acid (10 mg. per day). Four days after the start of folic-acid therapy the reticulocyte count had risen from 2.5% to 46.5%, and the haemoglobin rose slowly to a maximum of 6 g./100 ml. There appeared to be a second reticulocyte response from treatment with oral iron.

Case 4

This infant was 10 months old when first seen in the paediatric out-patient department. She had had fever, a cold, and slight diarrhoea for a few days. Two months later she was admitted to hospital because of recurrent infections of the upper respiratory tract, associated with fever, and malnutrition. She had been breast-fed for three months, and then weaned on to skimmed milk supplemented with carrot juice and potato.

On examination she was miserable and malnourished—weight 13 lb. 15 oz. (6.3 kg.). The temperature was 103° F. (39.4° C.). The hair was sparse and silky, but there was no oedema. The liver-edge was just palpable, and the spleen was enlarged two fingerbreadths. There was no jaundice. A blood transfusion of 300 ml. was given. Haemoglobin electrophoresis on a post-transfusion sample of blood showed an S + A pattern (approximately 70% haemoglobin S and 30% haemoglobin A). It was thought likely that this represented the pattern of sickle-cell anaemia plus a minor fraction of normal haemoglobin derived from the transfused blood.

A bone-marrow aspiration revealed intense erythroid hyperplasia with some megaloblastic changes, and consequently treatment with folic acid (10 mg. per day) was begun. The reticulocyte count rose from 9% to 32% seven days later, and the haemoglobin level rose from 6.2 to 8.2 g./100 ml. in the same period.

Case 5

A female infant aged 13 months was admitted to hospital because of swelling of the ankles for one week and vomiting and diarrhoea for four days. She had been breast-fed twice daily, supplemented with "lactogen," for eight months, and then weaned on to oat porridge and condensed milk with an occasional addition of some skimmed milk to the porridge. Three months before admission to hospital she was seen in the casualty department because of fever and vomiting. She was noted to be undernourished at that time and suffering from an upper respiratory infection. She was put on skimmed milk, and when seen again on two occasions she seemed to be improving. However, she was noticed to be pale, and cod-liver oil and iron were given.

On examination she was malnourished—weight 11 lb. 6 oz. (5.2 kg.)—and moderately wasted. She was slightly dehydrated but afebrile. Her mucous membranes were very pale, and there was some bilateral oedema of the ankles. The skin on the legs was dry and cracked; the hair was sparse but not depigmented. There was no jaundice. The liver was palpable 1½ in. (4 cm.) below the costal margin, but the spleen was not felt. There was no lymphadenopathy. Type S haemoglobin only was found on electrophoresis. Bone-marrow aspiration showed that erythropoiesis was megaloblastic in type. A diagnosis of sickle-cell anaemia complicated by megaloblastic anaemia was made.

An immediate blood transfusion of 100 ml. was given, followed by intravenous fluids. The vomiting was controlled by gastric lavage, and oral feeds were begun with clear fluids followed by gradually increasing strengths of skimmed milk. Folic-acid therapy (10 mg. per day) was begun on the

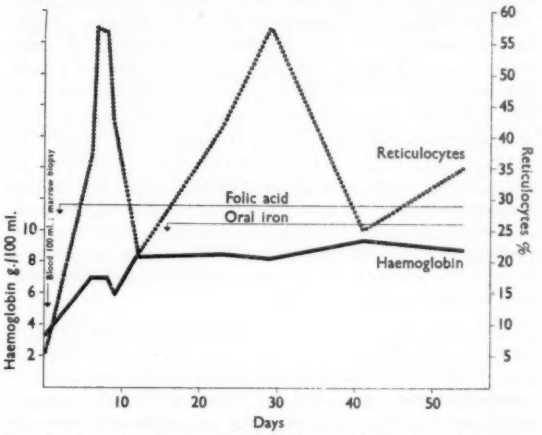

FIG. 6.—Case 5. Curves from serial haemoglobin and reticulocyte estimations.

second day, and six days later the reticulocyte count had risen from an initial value of 5% to 58% (Fig. 6). The haemoglobin level rose to 8.4 g./100 ml., and remained at about that level during the rest of her stay in hospital. A second, very marked reticulocyte response was noted as a result of oral iron. There was no significant further increase in haemoglobin.

Discussion

The incidence of sickling in a typical population group in Jamaica is 11% (Went, 1957), and one would therefore expect 3 cases of sickle-cell anaemia per 1,000 births. The fact that in a series of 50 cases of megaloblastic anaemia of infancy five were also suffering from sickle-cell anaemia is therefore highly significant, and it is likely that in Jamaica infants with sickle-cell anaemia are unusually prone to develop megaloblastic anaemia. The constant regenerative effort associated with the haemolytic process may be assumed to create a very heavy demand for haemopoietic substances, so that if there is an inadequate intake of such substances, or a diminished absorption as may occur with diarrhoea, a megaloblastic anaemia may result. This situation is even more likely to occur when the demand for haemopoietic substances is increased, as in periods of rapid growth and in pregnancy.

In megaloblastic anaemia of infancy it seems likely that the deficiency is mainly one of folic acid. The dietary intake of folic acid in infants in Jamaica must

be very near the borderline of adequacy in the post-weaning period. Milk, which is normally the chief staple of an infant's diet during the first year of life, has a low folic-acid content, and the Jamaican infant receives little or no fresh milk and only small quantities of condensed milk. The heating processes involved in the canning and powdering of milk further reduce the already low content of folic acid (Luhby and Wheeler, 1949). Three of the cases (Nos. 1, 4, and 5) were suffering from frank malnutrition which was comparable in degree to what is seen in other infants with megaloblastic anaemia. The other two cases, however, were moderately well nourished as judged by weight, but had been refusing their feeds during the three to four weeks previous to admission.

The only supplementary foods given to four out of the five infants were some cereals. Case 2 received a comparatively good diet, but green vegetables and meat, which are the best sources of folic acid, were not given. Though dietary inadequacy is probably the main factor in the aetiology of the megaloblastic anaemia in these five cases, it is likely that infection also played a part. The importance of infection in precipitating the condition has been stressed, and an increase in the requirements of ascorbic acid in infection is thought to be responsible (May *et al.*, 1952). The infection may sometimes be quite trivial and may have subsided with or without treatment before the anaemia becomes evident. Attacks of vomiting and diarrhoea, together with feeding problems, and mild infections of the upper respiratory tract were present in various combinations in the five cases described in this paper.

The most striking feature with regard to these children from a clinical point of view was the severe anaemia (see Table, p. 775). The average haemoglobin level on admission was 3.4 g./100 ml., which contrasts strikingly with our findings in 114 cases of sickle-cell anaemia (Went and MacIver, 1956; MacIver and Went, 1958; Went and MacIver, 1958), in which the average haemoglobin level was found to be 7.2 g./100 ml. In the 0–2 year age-group (19 cases) the average haemoglobin level was about the same (7.5 g./100 ml.) when four very low values due to associated megaloblastic anaemia were excluded. In addition, in our five cases with associated megaloblastic anaemia the reticulocyte counts were definitely lower (average 7%) than is usual in sickle-cell anaemia in this age-group (average 20.5%). Treatment with folic acid produced a very striking increase in the reticulocyte counts in every case, with a maximum response in an average of seven days after the start of folic acid therapy (see Table). A rise of haemoglobin followed to an average of 7.2 g./100 ml. and a fall in reticulocytes to an average of 26%, both of which must be regarded as normal values in sickle-cell anaemia.

The bone-marrow morphology varied from a gross megaloblastic change in Cases 1 and 2 (Figs. 2 and 4) to a less markedly abnormal, but none the less characteristic, picture in the other three cases. Nucleated red cells were often numerous in the peripheral blood, and in Cases 2 and 3 many of these were clearly megaloblasts.

Case 1 (Fig. 3) was of particular interest, since it was possible to measure the half-life of transfused red cells in his circulation. After the transfusion of 180 ml. of blood at the beginning of his first admission, his haemoglobin fell in eight days from 6.2 to 3.6 g./100 ml. (Fig. 3). Since this is a very quick breakdown we can assume that the destroyed red cells were mainly his own cells containing haemoglobin S only; it is well known that sickle-cell-anaemia red cells have a very much shortened survival time. This child came to hospital with a haemoglobin of 2.8 g./100 ml. and lost 2.6 g./100 ml. in eight days. It is therefore reasonable to assume that when he was discharged after the first admission, having had two further blood transfusions, only an insignificant amount of his own red cells remained. In addition, his reticulocyte count during his first admission remained low with the exception of one small peak probably caused by the intravenous iron which was administered; there was also folic-acid deficiency, however, which prevented the reticulocyte response to iron being any higher or of longer duration.

Fifty-nine days after the last transfusion, when he was readmitted, the haemoglobin level had fallen to 6.3 g./100 ml., which shows the life-span of the transfused red cells to be approximately 120 days. Fig. 3 shows that the rate of disappearance of the transfused red cells (haemoglobin A) in the 26 days after readmission was not significantly different from that in the 59 days between admission. This was calculated from quantitation of electrophoretic strips on days 6 and 19 after the onset of folic-acid therapy, when respectively 35% haemoglobin S and 86% haemoglobin S were found. On the second occasion 5% haemoglobin F also was present, leaving about 10% haemoglobin A from the original transfused cells. From these findings it is clear that no extracorpuscular defect producing an excessive destruction of normal cells was present in this case. Sprague and Paterson (1958) have suggested the possibility of such a mechanism in one case, but give no data to support it.

An unexpected finding in three cases (Nos. 3, 4, and 5) was the occurrence of an additional reticulocyte response with iron therapy (Fig. 6) (in Case 4 the iron was given first). In no case, however, was there any significant further increase in haemoglobin level. Presumably the increase in erythropoiesis was balanced by an increased rate of destruction.

Iron stains of sections of bone-marrow in all five cases were also interesting. Only in Case 1 was abundant iron present, but this infant had received a total of 550 ml. of blood, as well as a course of intramuscular iron, and in addition for two months had made scarcely any erythrocytes of his own. The reticulocyte response to folic-acid treatment in Case 1 cannot therefore have been in any way influenced by the simultaneous administration of oral iron. In Cases 4 and 5 a trace of iron was present in the marrow, but both these children had recently received blood transfusions. In Cases 2 and 3 no iron was detectable at all in the marrow. It would therefore seem that these four infants were deficient of iron as well as of folic acid. This is rather difficult to explain, since an increase in stainable iron in the marrow is usual in haemolytic anaemias. One can only suppose, therefore, that there was also a marked nutritional deficiency of iron in these cases. But in our experience such a deficiency is not usually striking in the straightforward megaloblastic anaemia of infancy. Iron therapy may be required in the course of recovery to produce sustained improvement, but any initial response to iron is negligible, and double reticulocyte responses when iron is given after folic-acid therapy have not been noted.

When patients with sickle-cell anaemia are seen with anaemia of a greater severity than is usual for this disease (as in our five patients) many investigators might

be inclined to ascribe the fall in haemoglobin to a haemolytic crisis. Such a haemolytic crisis must be distinguished from the aplastic crisis described by Singer *et al.* (1950) and from the painful crisis. The latter appears to be due to erythrostasis from sickled red cells, and is commonly observed in bones, joints, and the abdomen (Golding *et al.*, 1959). Diggs (1956) has given good evidence that there is no increased destruction of red cells in the painful crisis, nor in any other acute episode related to sickle-cell anaemia. Our own experience seems to confirm this view: we have never observed a haemolytic crisis, and when we have seen an exacerbation of jaundice this has been accompanied neither by a fall in haemoglobin nor by a rise in reticulocyte count. Only once have we observed an aplastic crisis, and, in Jamaica at least, a "megaloblastic crisis" seems to be the major cause of such severely anaemic episodes in young children with sickle-cell anaemia.

Summary

In a series of 50 cases of megaloblastic anaemia of infancy five cases with associated sickle-cell anaemia were seen.

These cases presented with unusually low haemoglobin and reticulocyte levels for sickle-cell anaemia, and the bone-marrows were megaloblastic. Folic-acid therapy produced a dramatic increase in reticulocytes and a rise in haemoglobin to the level normally seen in sickle-cell anaemia. Some degree of associated iron deficiency was present in three cases.

In one of the cases described it was possible to measure the half-life of transfused erythrocytes with reasonable accuracy. The cell survival was found to be normal.

The question of crises in sickle-cell anaemia is discussed.

ADDENDUM.—Between November, 1959, and February, 1960, we have seen five more cases of sickle-cell disease with aplastic crises. Three of these were in one family in which a child with sickle-cell anaemia was affected. Three weeks later his sister with sickle-cell anaemia also had an aplastic crisis (Hb 1.8 g./100 ml.), and after another two weeks their mother, suffering from sickle-cell/haemoglobin C disease, had to be admitted with a combination of an aplastic and painful crisis.

We are grateful to Dr. E. H. Back, under whose care these infants were, for allowing us to see them and for making the case-notes available to us.

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SPHEROCYTIC ANAEMIA, COMPLICATED BY MEGALOBLASTIC ANAEMIA OF PREGNANCY

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The association of congenital spherocytic anaemia (acholuric jaundice) with megaloblastic anaemia during pregnancy has been recorded by Davidson (1952), by Drury and Geoghegan (1957), and by Giles and Shuttleworth (1958). A further case with this association in two successive pregnancies is here reported.

Case History: First Pregnancy

A primipara aged 27 was admitted in labour as an emergency with toxaemia in the 40th week of pregnancy. She had previously enjoyed good health; there was no history of jaundice or any relevant family history. The pregnancy had proceeded normally—under regular medical supervision—until about two weeks before admission, when she became pale, easily tired, and short of breath; oedema of ankles, albuminuria, and an increase in blood-pressure were found.

On the day before admission the membranes had ruptured, discharging meconium-stained liquor. Examination showed pallor of the skin and mucous membranes and marked oedema of face, ankles, and abdomen. Cardiovascular and respiratory systems were normal, with blood-pressure 150/75, pulse 92, and temperature 99° F. (37.2° C.). The urine contained a moderate amount of albumin. A healthy boy, weighing 7 lb. 15 oz. (3,600 g.), was born 12 hours after the onset of labour. The placenta was grossly infarcted; the membranes were complete. Blood loss was less than 1 pint (570 ml.).

A blood count after delivery was as follows: Hb, 4.4 g./100 ml. (30%); red cells 2,370,000; C.I., 0.65; white cells, 22,100 (polymorphonuclears 81%, lymphocytes 15%, myelocytes 4%). The red blood cells were microcytic and hypochromic with marked anisocytosis and poikilocytosis; many showed polychromasia and punctate basophilia. There were eight normoblasts to 100 white blood cells.

Cultures of a catheter specimen of urine, and a high vaginal swab yielded a growth of coliform bacilli. After delivery blood-pressure was 130/70, pulse 128, and temperature 99.6° F. (37.6° C.) in the evening, which was not influenced by treatment with penicillin, sulphadimidine, or streptomycin. Three pints (1,700 ml.) of blood was transfused, but one week later a further count showed no great improvement. The white blood cells, however, had fallen to 2,850/c.mm.

Bone-marrow examination revealed a highly cellular marrow with many megaloblasts. A diagnosis of megaloblastic anaemia of pregnancy was made, and 100 mg. of folic acid was given by mouth for the first three days. Reticulocytes rose to 27% and the general condition improved. She was then transferred to a general hospital for further investigation. Clinical examination confirmed a grade I splenomegaly. Laboratory examinations showed increased corpuscular fragility and bilirubinaemia varying between 1 and 1.6 mg./100 ml.; other liver-function tests were essentially normal. Faecal fat excretion on a 50-g. daily intake over six days was normal, and free HCl was present in the gastric contents. Microspherocytes were

consistently present in the blood films and reticulocyte counts showed marked daily variations (5–23%) unrelated to treatment.

The patient was discharged home feeling well but still with splenomegaly and anaemia, a blood count of 3,200,000, and Hb 9.3 g./100 ml. Further observations over the next 12 months showed no essential change. Splenomegaly, bilirubinaemia, and increased osmotic fragility persisted. Splenectomy was refused and the patient failed to attend for further observation.

Second Pregnancy

The patient was next seen six years later, as an emergency admission to the Birmingham Maternity Hospital in the 29th week of her second pregnancy. In the interval she had been in good health and had remained so during her second pregnancy until two weeks before admission. She then began to look pale and feel increasingly tired, with shortness of breath. Examination was negative apart from a palpable spleen and marked pallor; blood-pressure 130/80, pulse rate 92, and temperature 98.6° F. (37° C.). The urine contained a trace of albumin. The uterus corresponded in size to that of a 26-weeks pregnancy. Foetal movements and heart sounds were present.

Investigations.—Blood count: Hb, 5 g./100 ml. (34%); red cells, 997,000; C.I., 1.7; white cells, 6,800; P.C.V., 11%; M.C.V. 110 cubic microns; M.C.H.C., 45.5%. Stained film: "typical late megaloblasts are present in small numbers." Schumm's test for methaemalbumin was positive and haptoglobin was absent from the electrophoretogram, indicating active haemolysis. Serum iron, 0.265 mg./100 ml.; serum protein, 6.4 g./100 ml. (albumin 3.3 g., globulin 3.1 g.); serum vitamin B_{12} (*Lactobacillus leichmannii* method), 40 $\mu\mu$g./ml.

Treatment

Folic acid, 20 mg. daily, was given by intramuscular injection for nine days. On the day after admission the patient's haemoglobin fell to 4.4 g./100 ml. (30%), and next morning her temperature rose to 102° F. (38.9° C.). She collapsed, and 2 pints (1,140 ml.) of cross-matched blood was transfused. Foetal heart sounds were now no longer perceptible. The serum-iron level had fallen to 0.111 mg./100 ml., suggesting a therapeutic response to folic acid, while the reticulocytes reached a peak of 15% four days after the start of treatment.

In view of the low serum level of vitamin B_{12}, a dose of 100 μg. of cyanocobalamin was given on two separate occasions. On the ninth day the haemoglobin level was 10 g./100 ml. (68%).

Progress

A red-cell fragility test showed diminished osmotic resistance. At her own request the patient was discharged to continue to take folic acid by mouth. Improvement was maintained at home until the 32nd week of pregnancy, when it was noted that the uterus corresponded in size to a 24-week pregnancy. A positive Spoulding sign confirmed the death of the foetus. Repeated examinations of the fibrinogen levels were made, but at no time did the level fall below 200 mg./100 ml. A mild but definite jaundice was noted clinically for the first time, while the serum bilirubin varied between 2 and 2.5 mg./100 ml. A reticulocytosis of 12% was also noted, which could not be accounted for as a therapeutic response. Repeated examinations confirmed the abnormal osmotic fragility of the red cells. The serum vitamin B_{12} level had fallen to 75 $\mu\mu$g./ml.

In the 34th week of pregnancy the patient was delivered at home of a macerated stillbirth. The post-mortem appearance of both foetus and placenta was consistent with intrauterine death at the 28th to 30th week of pregnancy, that is, the period of severest anaemia of the mother.

Ten days post-partum, the patient was seen at the out-patient department, feeling very well, though blood counts were still abnormal (R.B.C., 3,450,000; Hb, 10 g./100 ml.) and a blood film indicated excessive erythropoietic activity. The serum bilirubin was still elevated at 1.4 mg./100 ml. The patient remained steadfast in her refusal of splenectomy and declined further blood examinations. She was visited a year later by a health visitor, who found her in good condition, but failed to persuade her to attend at the follow-up clinic, nor was it possible to check the patient's relatives for the presence of spherocytosis.

Comment

Our purpose in reporting this case is to emphasize the possibility of two types of anaemia occurring in the same patient and the need for full investigation in all instances of severe anaemia in pregnancy. It may not be sufficient to arrive at a diagnosis, but the response to treatment should be watched also. This case and the one reported by Drury and Geoghegan (1957) presented as megaloblastic anaemia of pregnancy. The spherocytosis was discovered when treatment with folic acid resulted in considerable improvement but failed to bring about the usual return to normality.

The cases described by Davidson (1952) and by Shuttleworth and Giles (1958, personal communication), on the other hand, were diagnosed as cases of haemolytic anaemia before any pregnancy anaemia had developed. In both instances the observers were particularly interested in the study of megaloblastic anaemia, and thus diagnosed the complication promptly.

It is, however, quite possible that a number of such combinations are missed. A patient diagnosed as suffering from megaloblastic anaemia of pregnancy and improving on folic acid therapy may well be lost sight of after delivery. Conversely, a woman with known congenital haemolytic anaemia has a convenient explanation for any exacerbation that may occur in pregnancy, and consequently further investigation is shelved.

The close causal association between the congenital haemolytic anaemia and the complicating megaloblastosis is demonstrated by Drury and Geoghegan (1957). Their patient had developed megaloblastic anaemia in two consecutive pregnancies prior to splenectomy, but not in a third pregnancy which occurred afterwards. Our patient, by refusing splenectomy, did not give us an opportunity of confirming these observations. Two patients, however, have been observed in this centre who had had previous splenectomies for congenital haemolytic anaemia. Neither showed any tendency to develop a megaloblastic anaemia when pregnant.

The nature of the deficient factor in megaloblastic anaemia of pregnancy is still uncertain. The response to folic acid therapy and the low serum levels of vitamin B_{12} in our patient suggest that these vitamins were subject to increased demands. Davidson considered that "it is reasonable to suppose that the additional strain of pregnancy led to the development of megaloblastic anaemia by increasing the needs for haemopoietic factors in a patient whose requirements were already greater than normal because of pre-existing haemolytic anaemia."

Summary

A further case is reported of complication of congenital haemolytic anaemia by megaloblastic anaemia. This happened in two consecutive pregnancies more than six years apart. The patient had no symptoms of haemolytic anaemia when not pregnant or puerperal.

The existence of congenital spherocytosis was suspected only when a persistent irregular reticulocyte response was observed after treatment with folic acid.

We are grateful to Professor H. C. McLaren for permission to publish details from the case notes of the first pregnancy, and to Mr. A. L. Deason from those of the second pregnancy. The haematological investigation after our patient's first confinement was carried out by the late Dr. A. L. Peeney. We are further indebted to Dr. Eileen Shuttleworth for detailed clinical and haematological information on a similar case.

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MYELOMATOSIS WITH LIPAEMIA AND XANTHOMATA

BY

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When a patient develops two rare disorders at the same time it is natural to look for a common factor between them, especially when one hears that they have occurred together in other patients. A patient simultaneously developed extensive xanthomatosis and myelomatosis. The association of myelomatosis with hyperlipaemia seems to be a real one, but I have failed to explain it. This paper presents the results of investigations and a brief review of other cases.

Case Report

A woman of 65 who had previously been healthy began, in 1955, to experience shortness of breath and pain in the chest on exertion. Six months later she suffered a prolonged attack of chest pain typical of myocardial infarction. During convalescence she noticed a yellow discoloration around her eyes and later in the palmar creases. Both she and her husband were certain there had been no trace of yellowness before. From that time the slightest exertion caused severe pain in the chest, and a year after the beginning of her symptoms a second severe attack of cardiac pain occurred, for which she was admitted to hospital. During the preceding weeks she had noticed increasing pallor and some loss of weight. None of her family had a history suggesting xanthomatosis or early coronary artery disease.

On admission she was strikingly pale, with arresting bright-yellow plaques round her eyes. The whole skin surface was infiltrated with this yellow material, which condensed into soft impalpable plaques over the extensor surface of joints and in the palmar creases as well as round her eyes. The thickest plaques were bright orange; when the skin was stretched over them skin markings could still be seen. Small tuberous yellow swellings were present on the abdomen and buttocks. There were no xanthomata of the tendons.

Except for a pericardial friction rub, heard on the day after admission, there were no other abnormal findings. An electrocardiogram confirmed the clinical diagnosis of myocardial infarction.

Cause of the Anaemia

On admission the patient's haemoglobin was 6.5 g./100 ml. with a mean cell haemoglobin concentration of 31%. The normal Hb content of the cells and the fact that her stools contained no occult blood made bleeding as a cause of the anaemia unlikely. The sedimentation rate was 160 mm. in the first hour (Westergren) and blood films showed excessive rouleaux formation. Marrow smears from both sternum and iliac crest showed a diffuse infiltration with abnormal plasma cells—mostly primitive nucleolated forms—some binucleate and some showing mitotic abnormalities. A representative nucleated-cell count contained 36% of plasma cells. Repeated marrow studies over the next two years gave similar appearances.

An attempt was made to stain the plasma cells in the marrow smear with an aqueous fat stain. It was necessary to wash freshly aspirated marrow in saline to remove the lipaemic plasma. Bovine albumin was used to stick the washed cells to a slide. The smear was then stained with a saturated solution of scharlach R III and counterstained with 1% aqueous methylene blue. A few fat droplets accidentally deposited on the slide were stained red, but no droplets of fat were seen in the plasma cells.

During her first admission neither *x*-ray nor biochemical findings suggested bone disease, but films taken two and a half years later showed typical punched-out areas of bone destruction in the skull and the sixth left rib. There was no protein or Bence Jones proteose in the urine. No cryoglobulins were present in the blood. At first a diagnosis of myelomatosis as a cause of the anaemia could only be tentative; as the course of the illness unfolded the diagnosis became certain.

Lipids in the Blood and Skin Nodules

The fasting serum was turbid with many chylomicra; heparin, 5,000 I.U. intravenously, did not alter this turbidity. All the lipid fractions of fasting-serum were increased (total

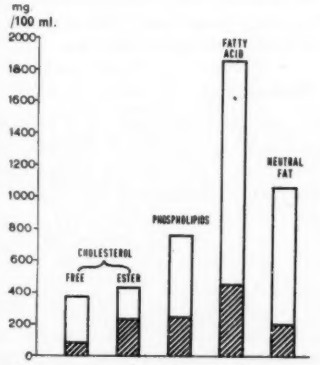

FIG. 1.—Fractionation of the serum lipids, showing that all fractions were increased. (Analysis kindly performed by Mr. N. Bell.) Hatched columns represent the normal upper limit.

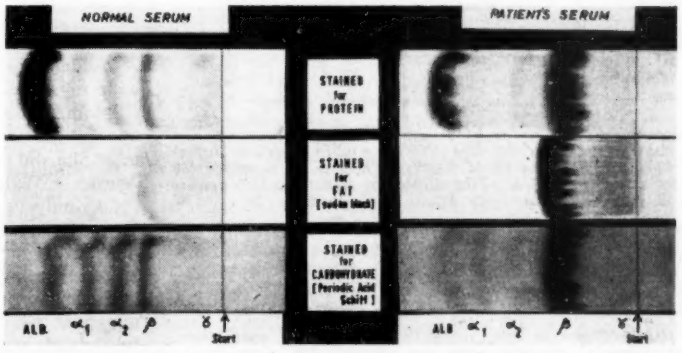

FIG. 2.—Electrophoresis of patient's serum, showing heavy staining for protein, fat, and carbohydrate in the β_2-globulin zone. The fat-staining zone migrated a little faster than the zone staining for protein and carbohydrate.

4.5 g./100 ml. instead of the normal 1.2 g./100 ml.) (see Fig. 1). Biopsy showed that the skin nodules stained strongly for neutral fat and were composed of aggregations of foam cells. The serum bilirubin, fasting blood sugar, and radio-iodine studies of thyroid function were normal. No studies were made on the rate of lipid clearance from the blood.

Serum Proteins

Paper electrophoretic strips (Fig. 2) stained for protein with lissamine green (Discombe *et al.*, 1954) showed an abnormal β_2-globulin band, and this zone also stained for carbohydrate with periodic acid Schiff reagent (Köiw and Grönwall, 1952). Just in front of this band was a zone which stained heavily for fat with Sudan black (Swahn, 1953). Dr. C. B. Laurell kindly estimated the different serum-protein fractions by paper electrophoresis as follows: total protein, 11 g./100 ml. (albumin 4 g., α_1-globulin 0.3 g., α_2-globulin 0.4 g., β_1-globulin 0.3 g., β_2-globulin 5.7 g., γ-globulin 0.3 g.). He found that the abnormal β_2-globulin contained about 6% of polysaccharides, half of which was hexose. The presence of carbohydrate in abnormal myeloma proteins has been noted previously (Sachs *et al.*, 1954; Osserman and Lawlor, 1954). Dr. K. W. Walton measured the cholesterol content of the α and β zones (Nury and Smith, 1957) and found that only 30 mg. (normal 30–70 mg./100 ml.) of the total serum cholesterol of 830 mg./100 ml. was in α-lipoprotein while the remaining 800 mg. (normal 150–230 mg./100 ml.) was in β-lipoprotein. Thus paper electrophoresis revealed an abnormal β_2-globulin in high concentration and nearly four times the normal β-lipoprotein concentration.

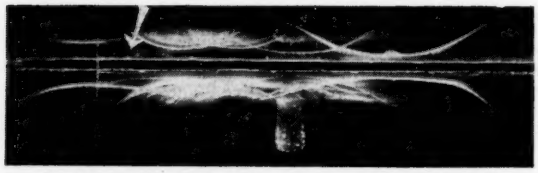

FIG. 3.—Immuno-electrophoresis showing an abnormal precipitation line (marked with arrow) in the β-globulin position. (Reproduced by courtesy of Dr. Ch. Wunderly.)

These findings were extended by immunological methods. Using a gel-diffusion technique (Gell, 1957) and a specific antiserum for human β-lipoprotein, Dr. J. F. Soothill found that the serum contained qualitatively normal β-lipoprotein in about double the usual concentration. Immuno-electrophoresis, kindly performed by Dr. Ch. Wunderly and Dr. J. F. Soothill, showed an abnormal precipitation line in the β-globulin position (Fig. 3).

TABLE I.—*Analysis of Low-intensity Lipoprotein Fractions Separated at Density* 1.063. *Normal Values Obtained from Gofman et al.* (1954*a*). (*Analysis Kindly Performed by Dr. J. W. Gofman*)

Fraction	Patient	Upper Limit of Normal
Sf^0 0–12	576 mg./100 ml.	642 mg./100 ml.
Sf^0 12–200	427 ,, /100 ,,	202 ,, /100 ,,
Sf^0 20–100	1,241 ,, /100 ,,	237 ,, /100 ,,
Sf^0 100–400	165 ,, /100 ,,	111 ,, /100 ,,

TABLE II.—*Concentration of Serum Protein Components Separated in the Ultracentrifuge* (60,000 *r.p.m. in Barbitone Buffer, pH* 8.6, I=0.05+0.2 *M NaCl*). *There is an increased S*·7 *Component Which is Not Altered by Removing Low-density Lipoprotein.* (*Analysis kindly performed by Dr. D. R. Stanworth*)

Component	Whole Serum	Serum Fraction Freed from Low-density Lipoprotein
S19	Trace	—
S9	0·47 g./100 ml.	0·42 g./100 ml.
S7	4·23 ,, /100 ,,	4·62 ,, /100 ,,
S4·5	3·54 ,, /100 ,,	2·62 ,, /100 ,,
Total	8·25 ,, /100 ,,	7·66 ,, /100 ,,

By adjusting the density of the medium, lipoproteins can be made to float in the ultracentrifuge while other proteins sediment. Dr. J. W. Gofman and Dr. K. W. Walton kindly undertook this study (Table I), and found a great increase of low-density β-lipoproteins (two to four times normal) but no increase of high-density (HDL-2 and HDL-3 of Gofman) α-lipoprotein. Dr. D. R. Stanworth analysed in the ultracentrifuge whole serum and serum freed from low-density lipoprotein. He found that the $S_{20}4.5$ component (mainly serum albumin) was reduced and that there was an increased $S_{20}7$ component which was apparently not affected by first removing the low-density lipoprotein (Table II). Only traces of S19 (macroglobulins) components were present. Similar results were found by Dr. J. W. Gofman, who also observed an appreciable and unusual $S_{20}9$–15 component.

Investigation of Family.—The patient had only two close relations: her daughter's serum cholesterol was 213 and her sister's 279 mg./100 ml. Paper electrophoresis showed a normal protein pattern in both of them.

Course and Treatment

She recovered uneventfully from her acute illness and her haemoglobin level was then maintained at about 8 g./100 ml. by blood transfusions every few months. Attempts to reduce the lipaemia were unsuccessful. A diet containing only 30 g. of fat daily had no effect. Treatment with sunflower-seed-oil emulsion (iodine number 122) produced a fall in the serum cholesterol from 800–900 mg./100 ml. to about 600 mg./100 ml. This emulsion was unpalatable, it did not affect her xanthomata, and it increased her weight, so it was stopped after three months. Treatment with triiodothyroacetic acid did not affect the serum cholesterol level or cause angina.

After two years of freedom from symptoms she developed incapacitating anginal pain and continuous back pain; *x*-ray films now showed the areas of bone destruction described above. Despite further blood transfusions and treatment with diamidinodiphenylamine dihydrochloride (M & B 938), her condition steadily deteriorated, and she died three and a half years after her symptoms began.

Post-mortem Findings (Dr. A. Pomerance)

The internal organs showed no fatty infiltration, and the atheromatous plaques in the aorta and great vessels were not unusually extensive for a patient of her age. The left coronary artery showed a local occlusion by a calcified plaque, but the coronary arteries were otherwise little affected by atheroma. The heart muscle showed no obvious fibrosis. A mass, 4 cm. in diameter, projected into the pleural cavity from the sixth left rib and in two places the skull was completely eroded by tumour tissue; the tumours were composed of typical myeloma cells. The bone-marrow contained numerous abnormal plasma cells. The immediate cause of death appeared to be purulent bronchitis.

Discussion

Waldenström (1952) described the case of a woman with myeloma, lipaemic serum, and large increase of β_2-globulin on electrophoresis. Her fasting serum lipid was 1.9 g./100 ml. and serum cholesterol 580 mg./100 ml. She did not have xanthomata or coronary artery disease. Waldenström reviewed the literature and found only two similar, but poorly documented, cases. One of these had marked lipaemia (7.3 g./100 ml.), myocardial infarction, and myeloma, but no skin lesions (Brehmer and Lübbers, 1950). No analysis of the serum proteins was given. Hollan (1958) mentioned a patient who had myelomatosis, "with all the serum lipid fractions increased," and whose blood contained "an abnormal lipoprotein moving with the β_2-globulin

fraction." This patient's plasma cells stained for fat, unlike those of our patient. Frame (1960) describes the case of a patient with a history of repeated episodes of pneumonia who presented with xanthomatosis and anaemia. He was found to have hyperlipaemia (1.48 g./100 ml.), a raised serum cholesterol (550 mg./100 ml.), a total serum protein of 9.5 g./100 ml. with 5.5 g. of γ-globulin, and 70% of myeloma cells in the bone-marrow. Thannhauser's (1958) patient, who died of multiple myeloma at the age of 57, nearly 20 years after developing widespread yellow-orange "xanthomatosis" of the skin, differs in that his serum cholesterol and phospholipid concentration were normal.

Since 1952 several studies of serum lipids in myeloma have been published. Sachs *et al.* (1954) found that the total serum lipid was raised in 3 out of 11 patients (highest value 1.4 g./100 ml.) but none of these had an abnormal β-globulin in the blood. The total serum cholesterol in the two patients with an abnormal β-globulin was actually lower than normal. Lewis and Page (1954) found that the serum cholesterol of 24 patients with myeloma was lower than normal. Very low concentrations of lipoprotein were found by ultracentrifuge studies in four of the patients who showed an abnormal β-globulin. The lipoprotein concentration in all the patients was normal or low. Magalini *et al.* (1956) found a normal cholesterol level in four cases of myeloma with normal distribution of the cholesterol among the serum globulins. Nikkilä (1953) observed that two out of four patients with myeloma had raised γ-globulin levels in the blood and also high serum cholesterols (395 and 448 mg./100 ml.). A high proportion of β- to α_1-lipoprotein was found in three of the patients.

Snapper (Spain *et al.*, 1956) found no case of coronary occlusion among his extensive series of patients with myelomatosis. He and his colleagues compared the post-mortem coronary and aortic atherosclerosis in 104 cases of multiple myeloma with two control groups, one dying a violent death and the other dying from cancer. Those with multiple myeloma had less atherosclerosis than the other groups. Two of the few patients with advanced sclerosis had a high serum cholesterol level (300 and 314 mg./100 ml.). The serum cholesterol level in the other 15 patients in whom it was known was below 200 mg./100 ml. Some of these patients even had an abnormally low serum cholesterol—for example, 36 mg./100 ml.

It is possible that our patient had two diseases—"idiopathic hyperlipaemia" and multiple myeloma—both of which developed independently. Yet, because the two conditions came on within six months of each other, it seems more than likely they were associated, especially as it is unusual for "idiopathic hyperlipaemia" first to show itself after the age of 60 (Lever *et al.*, 1954; Malmros *et al.*, 1954). Her blood contained a high concentration of immunologically normal β-lipoprotein just as Gofman *et al.* (1954b) have found in other patients with xanthomata of skin and tendons. If the myeloma cells produced the lipoprotein, as they presumably produced the abnormal globulin, this might explain the association of the two disorders; I cannot offer any evidence either for or against this hypothesis.

Summary

A patient developed xanthomatosis and myelomatosis at the same time.

Her blood was lipaemic, containing a high concentration of β-lipoprotein.

An abnormal globulin was found. It migrated in the β_2-globulin position on electrophoresis, moved with the S7 component in the ultracentrifuge, and stained heavily for carbohydrate.

A possible association between hyperlipaemia and myeloma is discussed.

I thank Dr. Richard Asher for his help and permission to publish this case; and Drs. G. Discombe, J. W. Gofman, J. E. Lovelock, K. W. Walton, and Professor J. Waldenström for advice and help. In addition to those mentioned in the text, I thank Drs. A. W. G. Goolden, N. D. Gower, and H. Roberts, and Mr. D. N. Rossington for help with the investigations. The sunflower-seed-oil emulsion was supplied by Messrs. Duncan, Flockhart & Co., and the M & B 938 by Messrs. May and Baker. Fig. 2 is reproduced from the *Transactions of the Sixth Congress of the European Society of Haematology* by courtesy of S. Karger A.G.

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[Another salmonella sent to Colindale was identified as an organism called *Salmonella abony*.] "It so happened that our local medical officer of health remembered having read that this organism occurred in the alimentary tract of tortoises. So he visited the patient's home, and there, sure enough in the garden, he found a tortoise. It was hibernating, and the family readily agreed to the admission of this tortoise to hospital, and it is now asleep in the hospital laboratory. They are waiting for it to wake up, and I suppose one may say, 'be a good tortoise.' Then a specimen will be available from which they expect to discover *Salmonella abony*. The alimentary tract of the tortoise is alive with a whole tribe of these things that have caused quite a lot of human infection. One pathologist in the Public Health Laboratory Service runs a tortoise farm to collect them. It is a strange episode in human disease, but it is a very important one. Moreover, it is exceedingly difficult to get rid of, because the alimentary tract of the tortoise is exceedingly sluggish. It is necessary to put a tortoise into a thing called a tortorium, where it is kept for four or five years while it clears itself and frees itself from salmonella." (Speech by Lord Taylor, Public Health Laboratory Service Bill, February 4.)

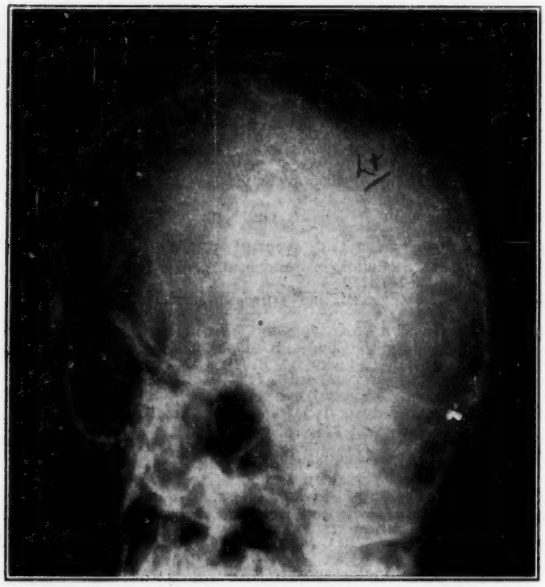
Medical Memoranda

Cerebellar Thrombosis after Carotid Ligation

Common carotid ligation may cause cerebral complications (Lambert Rogers, 1947), but brain-stem disturbances have not been reported to result from this procedure. Vascular thrombosis after angiography is not a rare complication (Dunsmore *et al.*, 1951; Perese *et al.*, 1954), but late thrombosis is unusual.

CASE REPORT

A woman aged 52 was admitted to hospital five days after the sudden onset of occipital headache, pain in the back of the neck and shoulders, transient confusion, and unsteadiness immediately after polishing a floor. Recurrent vomiting occurred for three days, and a moderate pyrexia settled by the fourth day. There was no past history of severe headache, but four years previously about eight bouts of severe stabbing pain in the distribution of the second



Left anterior oblique view of left internal carotid arteriogram, showing aneurysm at bifurcation of internal carotid.

division of the left trigeminal nerve had occurred, and at that time trigeminal neuralgia was suspected.

On examination her neck was stiff and Kernig's sign was present, but no other neurological signs were elicited nor was a cranial bruit heard. Blood-pressure was 150/90.

Lumbar puncture on the third day after onset showed a C.S.F. pressure of 220 mm., and the fluid was uniformly blood-stained with xanthochromic supernatant, indicating a recent subarachnoid haemorrhage.

Eight days after onset a right internal carotid arteriogram showed good filling, which demonstrated a normal vascular tree on this side. There was no satisfactory filling on the left side on this occasion, but a left vertebral arteriogram showed a normal basilar and posterior cerebral circulation, and the left posterior inferior cerebellar artery filled and could be seen arising from the left vertebral. Two days later a left internal carotid arteriogram demonstrated a large aneurysm on the bifurcation of the internal carotid (see Fig.).

Three days later (13 days after the subarachnoid haemorrhage occurred) the left common carotid was ligated.

The next day the patient was fully conscious, had good power in all limbs, and the C.S.F. was faintly xanthochromic with C.S.F. pressure of 170 mm. The fluid contained 123 erythrocytes, 2 lymphocytes, and 5 polymorphs per c.mm. Late on the third day after operation there was a sudden onset of occipital headache, drowsiness, vertigo, vomiting, and numbness in the right limbs.

In the ensuing 24 hours the following changes developed: (1) Coarse horizontal nystagmus, more marked to the left. (2) Left ptosis. (3) Absent corneal reflex and loss of superficial sensation in the trigeminal distribution on the left. (4) Slight left facial weakness. Transient loss of taste. (5) Transient tinnitus and deafness on the left. (6) Transient dysphagia. Deviation of the uvula to the right and low immobile pharyngeal arch on the left. Bulbar type of dysarthria. (7) Some deviation of tongue to the left. In the limbs, muscle power and tendon and superficial reflexes were normal. (8) The left limbs were grossly ataxic, with preservation of deep sensation on both sides. (9) Sensation of pinprick and temperature was impaired down the right side. The C.S.F. findings were not substantially altered.

A classical picture of posterior inferior cerebellar thrombosis on the left side had thus developed. Anticoagulants were begun, and slow subjective improvement took place with some lessening in the above signs.

COMMENT

To associate this posterior inferior cerebellar thrombosis with ligation of the left common carotid may entail postulating an established collateral circulation via the posterior communicating artery to a branch of the left vertebral in the absence of any obvious defect in the vertebral system and filling of the posterior inferior cerebellar from below, as demonstrated in the left vertebral arteriogram. Furthermore, after the operation a lapse of nearly three days occurred before the vascular accident.

A left vertebral arteriogram was carried out, but, though vascular thrombosis after angiography has been reported, in this case a week elapsed between the arteriogram and the event of thrombosis.

It is therefore tentatively suggested that the occurrence of posterior inferior cerebellar thrombosis either was due to late thrombosis succeeding the arteriogram or was entirely fortuitous.

My thanks are due to Dr. A. M. Stewart Wallace and to Mr. F. L. Davies for permission to report this case, and for advice concerning its production.

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The Annual Report, April, 1958–April, 1959, of the College of Physicians and Surgeons of Ontario reproduces as its frontispiece a caricature of Sir Henry Thompson, the London surgeon, who died in 1904 and who played a leading part in founding the Golders Green crematorium. He was cremated there when he died at the age of 82. The report also gives an interesting account of the College's history.

Reviews

SICK SOCIETY

Social Science and Social Pathology. By Barbara Wootton, assisted by Vera G. Seal and Rosalind Chambers. (Pp. 400. 35s.) London: George Allen and Unwin Ltd. 1959.

The necessities which have compressed people of all kinds into societies at a pace quite out of tune with organic evolution, and the relative unwillingness of people to pay the price for the security society gives by loss of individual freedom, do not make for harmony or perfection. This instability of the *milieu intérieur* of the body politic is accepted as common ground and lamented by reformers of all persuasions. Not only are all the qualities needed for fully responsible citizenship uncommonly present in one personality, but the corpus of civilization as a whole has an extensive pathology of its own. The description of social sickness is, in spite of the development of the social sciences, still everybody's business and the pointing out of evils accounts for a reckonable proportion of society's printed output. It is not to be wondered therefore, if the literature on want, crime, divorce, prostitution, idleness, and lack of socially acceptable aims suffers from political, theoretical, and theological bias, mixes fact with opinion, and is replete with prescriptions for treatment which may well be worse than the disease. The application of scientific method has at least cast some doubt on the firmly entrenched beliefs of previous generations and has attempted to improve the standard of fact-gathering. It has in some schools, in its preoccupation with methodology and facts for facts' sake, succeeded in squeezing the human interest out of a very human subject.

A long experience of social investigation and social reform in a vital period of their growth, and a reputation for bringing horse-sense to bear on problems that have become too theoretical, entitle Barbara Wootton to a very careful hearing, for this is her testament—her critique of the whole situation, given as a social scientist and as an individual with her own convictions. It is to her credit that she has managed to keep fact and opinion reasonably separate. It is her belief that the subject of delinquent or deviate behaviour is so charged with public feeling and sectional interest that no sense will emerge unless social science justifies itself by obtaining accurate and controlled information about those processes within society which discourage a responsible attitude in its members. Her presentation of this view involves the destruction of some fashionable concepts and attitudes to the subject. Although the main purpose of the book is not destructive, the author is not able to conceal her talents in this direction. Her own use of the available literature and her presentation of her own investigations are an example of the positive approach she recommends, and as such are its best advocate.

The book is divided into three parts. The first is concerned with information, including the statistics for different types of social pathology in England and Wales, and the results of investigations scientific and otherwise. The reports of committees and organizations dealing with antisocial behaviour are given as well as the data of the author's own investigations. The second part deals with contemporary attitudes towards delinquency and carries out a critical examination of 12 hypotheses as to its origin. In this section the appraisal of the influence of psychiatry and theories of individual psychodynamics is arresting, to say the least, as are her comments on the literature of psychiatric social work, which, she points out, fortunately bears little relation to the work done by the rank and file of this professional group. The third part is frankly opinion, and it allows for a fuller expression of the writer's feelings and personal dynamics. One has the impression of an orderly mind, a command of English rare in her field, and a few fine old-fashioned prejudices against psycho-analysts, eugenists, motorists, and the "working through" brand of social case-worker, not to leave out the do-gooders and lay dabblers in the soul-sickness of others.

The Baroness evidently embarked on her career as a convinced egalitarian, and she has ended it in the same spirit among her peers. Her view is that the major emphasis should be on the structure and function of society itself as the cause of anti-social reactions, rather than on the constitution of the individual. She has little time for problem-family studies such as have been promoted by the Eugenics Society, which comes in for some castigation. Her resignation from this body after a long membership was received just before the book was published. Much of her comment on the psychiatric contribution to criminology is richly deserved, and is adroitly achieved by condemnation from selected samples of its literature. She is, however, forgetful of the fact that psychiatry has grown up, even if it still has its voluble and fixated adolescents. It is sociology, surely, which now qualifies for the role of the mixed-up kid of the sciences.

This book is comprehensive; it is intelligent, pungent, readable, and often destructive; and it cannot be ignored. Those who come before the author's magisterial scrutiny cannot but profit from the emotions engendered from seeing themselves as Barbara Wootton sees them.

ALEXANDER KENNEDY.

VASCULAR SURGERY

Vascular Surgery. By Geza de Takats, M.D., M.S., F.A.C.S. (Pp. 726+ix; illustrated. £6 2s. 6d.) Philadelphia, London: W. B. Saunders Company. 1959.

During the past decade a number of textbooks have been written on the subjects of vascular and cardio-vascular surgery, but few have been of the standard of this fine contribution by Dr. G. de Takats. He deals with the problems of the diseases of the arterial, venous, and lymphatic systems of the limbs, the aorta, the extracranial portions of the cerebral arteries, and the surgical aspects of arterial hypertension.

The book has been written in four parts: the first is on fundamental principles; the second on methods of diagnosis; the third and longest on vascular syndromes requiring surgical care; and the fourth on surgical technique. While all sections are good, that on surgical technique is particularly impressive. Clear and well-drawn figures accompanied by a short descriptive text give the salient points of each operation.

To a reader from Europe a particularly pleasing feature is the author's familiarity with surgical practice on this side of the Atlantic Ocean. To take as an example the operation of upper thoracic sympathectomy: most American textbooks describe only the

posterior approach, but Dr. de Takats has included descriptions of this operation by both the cervical and axillary routes.

This book is well written, well illustrated, and well produced. It has been a pleasure to review, and it is strongly recommended.

C. G. ROB.

A PICTORIAL UROLOGY

Urology in Outline. By T. L. Chapman, Ch.M., F.R.C.S. (Eng.), F.R.F.P.S.(Glas.). (Pp. 176+vii; illustrated. 27s. 6d.) Edinburgh, London: E. and S. Livingstone, Ltd. 1959.

This is a short book of 170 pages designed for students and hospital residents. As an alternative to a short textbook giving summaries of how to investigate urological cases, and the signs, symptoms, and pathology of diseases of the urinary tract, the author has presented the subject in pictorial fashion, believing that many will learn the essentials more easily in this way.

The first three chapters deal with the symptoms of urological disorders, clinical methods of examination in urological patients, methods of urological investigation, and the essentials of renal function. Series of drawings illustrate diagrammatically those lesions of the urinary tract which may cause renal pain, conditions in the lower tract which are associated with urinary retention, the causes of haematuria and of pyuria, and the elements of the radiography of the urinary tract and of pyelography. These chapters are well done.

Most of the book is devoted to the commoner diseases of the upper and lower urinary tract, including urinary infections, tuberculous and calculous disease, hydronephrosis and renal tumours, and the common diseases of the prostate and of the bladder. Each chapter opens with two or more pages of descriptive text, and the subject is then handled pictorially, the drawings illustrating the pathology, symptoms, and diagnosis of the condition which is described. Only the most important operative measures are included, and these are very simply done. A useful chapter is included on the neurogenic bladder.

The book is a very useful one, especially for the student, who in these days is expected to read so many formal medical textbooks. The way the subject is presented should enable him to learn at least the essentials of the commoner urological disorders without much difficulty; the pictorial method may succeed in instilling into the mind a clinical picture of disease which more prosaic methods fail to do. The diagrams are simple to understand, the descriptive notes are adequately done, and the book is well produced.

L. N. PYRAH.

SEX EDUCATION

Sex, Love, and Society. By E. R. Matthews, M.R.C.S., L.R.C.P. (Pp. 199. 12s. 6d.) London: Victor Gollancz Ltd. 1959.

Dr. Matthews, once general practitioner and now a psychotherapist, has for some years given sex education to schoolboys and college students; this book represents a development of his lectures. The paper cover claims that this is not "just another sex book," and does so with some reason. The particular attraction of this work is that it places the physical and emotional aspects of sex in their proper context, as part of the whole personality of man and woman. This should make it much more valuable to those facing the problems of growing up, to those intending marriage, and to those who are concerned with the upbringing of a family.

The author emphasizes that harmonious marriage depends not so much on the partners making satisfactory bed companions as on their understanding of each other's basic outlook and instincts. In so doing he points out the less obvious manifestations of sex impulses, and traces the evolution of family life.

Although Dr. Matthews clearly has religious convictions, his arguments in favour of adherence to the moral code which obtains in Britain are based primarily on the interests of the individual and of the community as seen by a doctor. This is a pleasant and sane book, a corrective to some of the more lurid and so-called advanced views which disturb rather than help the younger generation.

T. N. A. JEFFCOATE.

ADVANCES IN VIROLOGY

Advances in Virus Research. Edited by Kenneth M. Smith and Max A. Lauffer. Volume VI. (Pp. 382. $10.) New York: Academic Press Inc. London: Academic Books Ltd. 1959.

Advances in Virus Research appears at intervals and consists of reviews of recent work in very rapidly developing fields of virology. These are often highly technical, but are written by experts for research workers in the same and closely related fields, and (despite the fact that they are often out of date almost before they appear) such reviews are extremely valuable. It is doubtful, however, if they will be appreciated by the average doctor who wishes to bring himself up to date painlessly in the clinical aspects of the subject.

Volume VI contains a comprehensive account of the physical and chemical structure of poliomyelitis virus, including a valuable analysis of studies on its inactivation, of great importance for safe production of the vaccine. There is also a review of current work on measles virus, which has only recently been cultivated in the laboratory. Of more general biological interest is an account of the physiology of bacteriophage growth taken from the marvellously detailed experimental findings which are now available. Three chapters relate to the purification, biochemistry, and spread of plant viruses; and finally there is an account of the killer particle, kappa, in *Paramecium*—a phenomenon which comes ever closer to the interests of virologists.

M. G. P. STOKER.

MEDICAL GEOGRAPHY

The Ecology of Human Disease. By Jacques M. May, M.D. Foreword by Felix Marti-Ibanez, M.D. (Pp. 327+xxi. $7.50.) New York: MD Publications, Inc. 1959.

This is the first volume of a three-volume work produced under the auspices of the American Geographical Society as a contribution to the study of medical geography. The aim has been to write a book useful to physicians, geographers, anthropologists, and social scientists, a fact which has necessitated a good deal of explanation and of repetition, some of it irksome to the medical reader. In this volume a number of transmissible diseases are considered, most of which would in this country be regarded as tropical in nature, though tuberculosis, scarlet fever, and measles are included.

The first chapters deal with the various factors affecting diseases in general. It is emphasized that in many instances a study of "the seed and the soil" is

not enough. Between these two may be one or more intermediaries whose life history and the conditions which influence it may be of paramount importance in spreading or controlling the disease. In the remainder and greater part of the book the agent, the host, and the mode of transmission of some individual diseases are shortly described, while the geographical distribution is discussed in more detail. There are several maps—some not too easy to elucidate—to show the incidence or spread of particular diseases or outbreaks of disease.

To the non-medical scientific worker this book will be useful as a reference volume of medical geography where he can easily find what facts are known about the incidence of various diseases in the part of the world in which he is interested. It is doubtful if the physician will find it of much value, for he will probably require more information about matters only cursorily dealt with, or he will want to go into the medical geography in more detail.

ALAN ROOK.

PROGRESS IN PSYCHIATRY

Recent Progress in Psychiatry. Volume 3. *The Journal of Mental Science.* Edited by G. W. T. H. Fleming and A. Walk. With the assistance of L. C. Cook, P. K. McCowan, M. Partridge, F. L. Golla, A. Meyer, W. Linford Rees, W. Warren, T. F. Main, R. M. Norman, and B. W. Richards. (Pp. 397; illustrated. 42s.) London: J. and A. Churchill Ltd. 1959.

This is the third of a series of specially written articles summarizing recent progress in psychiatry, the two previous volumes appearing in 1944 and 1950 respectively. The first two set a very high standard indeed, which this volume unfortunately does not live up to. Most of the important recent advances in psychological medicine have been in treatment. And often these have been of a quite empirical nature, though together they have recently constituted a revolution in psychiatric treatment. Unfortunately, this book has little at all to say about recent work related to any of these advances. E.C.T., insulin, and all the mass of work on the new tranquillizing drugs have been completely ignored. There is also nothing about psycho-analysis, group methods of treatment, or even about the uses of psychotherapy in general. Chapters on advances in the treatment of children and old people are also absent. Excellent articles, however, do appear on psychological testing, psychiatric genetics, and the biochemistry of the nervous system. But, again, much too much space has been wasted on topics about which very little is really known at the present time, such as the enzymatic basis of certain psychoses and the psychiatry of crime.

This book has been very useful in the past, and was again being eagerly awaited because of the generally high quality of its articles and the practical help it has given to the clinician. But the delay in the appearance of this third volume and its contents have both proved disappointing. One can only hope for better next time.

WILLIAM SARGANT.

A Synopsis of Skin Diseases, by Bethel Solomons, jun. (293 pp., 30s.), a newcomer to the synopsis series published by John Wright and Sons, Ltd., Bristol, is written as a short reference book for the practitioner, for those needing to revise the subject rapidly, and for the student preparing for his final examination. A table giving the concentrations of over 800 substances which can be used in patch testing, a short formulary, and a very full index are included.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Pediatric Neurosurgery. Edited by Ira Jackson, M.D., M.Sc., F.A.C.S., F.A.C.A., and Raymond K. Thompson, M.D., F.A.C.S. With 24 contributors. (Pp. 564+xvi; illustrated. £6 5s.) Oxford: Blackwell Scientific Publications. 1959.

Biochemistry of Blood in Health and Disease. By I. Newton Kugelmass, M.D., Ph.D., Sc.D. (Pp. 543+ix; illustrated. £6 6s.) Oxford: Blackwell Scientific Publications. 1959.

Night Vision. By Gaetan E. Jayle, Albert G. Ourgaud, L. F. Baisinger, M.D., and William John Holmes, M.D. (Pp. 408+xiv; illustrated. £5 8s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Essentials of Orthopaedics. By Philip Wiles, M.S.(Lond.), F.R.C.S.(Eng.), F.A.C.S. Third edition. (Pp. 576+xiii; illustrated. 70s.) London: J. and A. Churchill, Ltd. 1959.

Doctor's Weekend. By Hubert Bagster. (Pp. 191. 15s.) London: Andre Deutsch. 1960.

Surgery of Repair as Applied to Hand Injuries. By B. K. Rank, C.M.G., M.S.(Melbourne), F.R.C.S.(Eng.), F.R.A.C.S., and A. R. Wakefield, M.S.(Melbourne), F.R.C.S.(Eng.), F.R.A.C.S. Second edition. (Pp. 284+xiv; illustrated. 45s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

The Human Spine in Health and Disease. Anatomicopathologic Studies. By Georg Schmorl, M.D. ***Clinicoradiologic Aspects.*** By Herbert Junghanns, M.D. First American edition, translated and edited by Stefan P. Wilk, M.D., and Lowell S. Goin, M.D. (Pp. 285+xii; illustrated $21.) New York and London: Grune and Stratton. 1959.

La Colelitiasi et alia Hepatologica. Atti del Primo Symposium Internazionale di Epatologia, Chianciano-Terme, June 28-29, 1958. By 30 contributors. (Pp. 637; illustrated.) Edizioni Chianciano. 1959.

Miscellaneous Notes. By F. Parkes Weber, M.D., F.R.C.P., F.S.A. Fifth series. (Pp. 21. 5s.) London: H. K. Lewis and Co., Ltd. 1960.

L'Apparato Joideo: Anatomia, Fisiopatologia e Clinica (Ricerche ed Osservazioni Personali). By Lorenzo Marcucci. Collana di Monografie de "L'Ateneo Parmense" No. 3 (Pp. 165; illustrated.) Parma: Edizioni "L'Ateneo Parmense." 1959.

Physiology of the Retina and the Visual Pathway. By G. S. Brindley, M.A., M.D. (Pp. 298+xi; illustrated. 35s.) London: Edward Arnold (Publishers) Ltd. 1960.

Toxic Aliphatic Fluorine Compounds. By F. L. M. Pattison, M.A., Ph.D., F.R.I.C., F.C.I.C. (Pp. 227+xi; illustrated. 18s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Co. 1959.

Postvaccinial Perivenous Encephalitis. A Pathological Anatomical Study on the Place of Postvaccinial Perivenous Encephalitis in the Group Encephalitides (The Disease of Turnbull-Lucksch-Bastiaanse). By Ernst de Vries. (Pp. 181+vii; illustrated. 38s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Co. 1960.

La Malattia di Ebstein. By Giulio Sotgiu, with Sergio Lenzi, Mario Facci, and Marco Foscarini. (Pp. 133; illustrated. L. 3,500.) Bologna: Cappelli. 1959.

Culture and Mental Health. Cross-Cultural Studies. Edited by Marvin K. Opler. (Pp. 533+xxi. 61s.) New York and London: The Macmillan Company. 1959.

American Academy of Orthopaedic Surgeons. Instructional Course Lectures. Volume XVI. 1959. (Pp. 335; illustrated. £6.) St. Louis: C. V. Mosby Co. London: Henry Kimpton. 1959.

A Short History of Nursing. By W. R. Bett, M.R.C.S., L.R.C.P., F.R.S.L., F.S.A.Scot. Illustrated by Mona Moore. (Pp. 125. 12s. 6d.) London: Faber and Faber, Ltd. 1960.

The Equality of Women. By the Right Honourable the Lord Denning, Q.C. ***Eleanor Rathbone Memorial Lecture.*** (Pp. 16. 3s. 6d.) Liverpool: University Press. 1960.

Arthritis. Medical Treatment and Home Care. By John H. Bland, M.D. Illustrated by George Daly. (Pp. 208+xix; illustrated. 34s. 6d.) New York and London: The Macmillan Company. 1960

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY MARCH 12 1960

CARCINOGENIC RISKS OF IRON-DEXTRAN

Three years ago H. G. Richmond[1-4] reported that sarcomas developed in the rat at the site of intramuscular injection of the iron-dextran complex "imferon." This observation has now been fully confirmed, and the work extended, by A. Haddow and E. S. Horning.[5] In studies of the effects of repeated injection of trypan blue in inducing histiocytic tumours,[6] Richmond wished to use a negative control—that is, a substance which, equally with trypan blue, would be taken up by the reticuloendothelium, but without producing tumours. In the expectation that iron must be non-carcinogenic, he chose imferon (manufactured by Benger Laboratories Ltd.). Surprisingly, he then found the iron-dextran itself to be carcinogenic, observing 37 local sarcomas, with latent periods of 9–14 months, in 64 rats given the complex by repeated intramuscular injection. Haddow and Horning now report 20 sarcomas in 30 rats, and 27 sarcomas in 37 mice, given imferon by repeated injection subcutaneously. The component dextran in itself was inactive, again confirming Richmond's work.

These observations are not only of theoretical interest; they carry implications of great practical importance. Thus Haddow and Horning discuss the bearing they have on the general question of the carcinogenic action of metals. It is evident from their paper that the new observation has already provided a useful stimulus in several ways to the study of carcinogenic mechanisms. But it also sharply raises the practical problem to what extent the conclusions from animal experiment can fairly be applied to man. In particular, is there justification or not for continuing to use imferon in practice?

Clearly the greater part of animal experiment would be pointless if its conclusions were disregarded, or if there were no hope of transferring them to man. In reality, the cases are legion, in both experimental pathology and therapy, in which the lessons of experiment are directly applicable with benefit to human medicine. This is not to say that the demonstration of a carcinogenic hazard in a given species can be taken to imply the same hazard in another: there are numerous examples to the contrary. In the present connexion, Haddow and Horning also emphasize that the carcinogenicity of iron-dextran in the mouse and rat has been shown thus far only through the use of massive doses, and that each injection introduced an amount of iron that was several times the normal body content. Though such overloading certainly entails systemic changes, nevertheless they conclude there is no reason to believe that the carcinogenic reaction is dependent on these, or that it is other than a preponderantly local effect, which may indeed mainly be determined by that fraction of the dose which is poorly absorbed or locally retained. They also cite recent experiments by L. Golberg and his colleagues, of Benger Laboratories Ltd., in which repeated amounts of imferon, representing very many multiples of the "clinical dose," were administered to rats, mice, and other species without apparent effect on health. However, while it in no way compared with the much greater incidence of tumours reported both by Richmond and by Haddow and Horning, Golberg and colleagues undoubtedly obtained a small yield of tumours attributable to imferon in certain of their experiments.

Haddow and Horning conclude that the carcinogenic response is decided primarily by the absolute amount administered, and only secondarily, if at all, by the relation of this to body weight. They also consider that, even if negative results were to be obtained in mice with doses that bear the same relation to those used in man as do the body weights of mice and men, this would not necessarily in any way diminish a potential hazard attaching to the absolute amounts that are in fact administered to human patients. Moreover, a disturbing feature of the experiments of Richmond and of Haddow and Horning is the high yield of tumours in both cases. Even if the hazard to man is much smaller, it could still account for a large absolute yield of tumours in view of the numbers exposed.

Imferon was introduced by Benger Laboratories Ltd. on the basis of much careful research and development. In particular, extensive pharmacological studies of the factors in the local absorption and general distribution of such iron-polysaccharide complexes were carried out by Golberg and his colleagues, who also utilized the relatively low

[1] Richmond, H. G., *Scot. med. J.*, 1957, **2**, 169.
[2] —— *Brit. med. J.*, 1959, **1**, 947.
[3] —— in *Cancer Progress*, 1959, Vol. 1, London.
[4] Haddow, A., in *Ciba Foundation Symposium on Carcinogenesis: Mechanisms of Action*, 1959, p. 300, London.
[5] —— and Horning, E. S., *J. nat. Cancer Inst.*, 1960, **24**, 109.
[6] Gillman, J., and Gillman, T., *Cancer (Philad.)*, 1952, **5**, 792.
[7] Golberg, L., Smith, J. P., and Martin, L. E., *Nature (Lond.)*, 1957, **179**, 734.
[8] —— —— —— *Brit. J. exp. Path.*, 1957, **38**, 297.
[9] Beresford, C. R., Golberg, L., and Smith, J. P., *Brit. J. Pharmacol.*, 1957, **12**, 107.
[10] Golberg, L., and Smith, J. P., *Brit. J. exp. Path.*, 1958, **39**, 59.

immediate toxicity of iron-dextran to investigate the effects of excessive administration and massive overload.[7–10] Over the past five years, on account of its ready absorption from the intramuscular site and its low toxicity, the preparation has found a wide application in the treatment of human iron-deficiency anaemias, including those of pregnancy and rheumatoid arthritis. There must be general sympathy with any house of repute which unexpectedly finds one of its products, so carefully developed, attended by possible hazard. Yet in all such cases both the public and the profession have the right to expect the highest standards of responsibility and caution—a responsibility which is already very generally accepted and freely discharged.

In all questions of carcinogenic hazard from environmental sources it is necessary to preserve a balance of judgment, and certainly not to be stampeded. But in the present case—though further work is desirable and is in fact proceeding—it seems that the facts available are already more than sufficient as a guide to wise policy. We understand that the product is no longer being advertised in Great Britain, though it continues to be sold and prescribed. Surely this solution is not only unsatisfactory and illogical, but also perhaps dangerous from the point of view of the producers themselves. We cannot affirm the hazard to man, let alone measure it. Further, it well may be that imferon has a useful place in the treatment of such cases of iron-deficiency anaemias as are otherwise intractable in the elderly. But the existing evidence is certainly sufficient to warrant, and indeed to demand, its speedy withdrawal from any kind of general use in man.

DEFIBRINATION SYNDROME

Partial or complete depletion of the amount of circulating fibrinogen is an occasional complication of some obstetrical abnormalities. It is most commonly associated with accidental haemorrhage in the late stages of pregnancy.[1 2 3] It can also occur when the patient has carried a dead foetus for a long time *in utero*,[4] in cases of amniotic-fluid embolism,[5] and in association with hydatidiform mole[6] and abortion in the earlier stages of pregnancy. A similar state has been found after extensive thoracic operations,[7–9] in association with metastatic carcinoma of prostate,[6 10 11] and after incompatible blood transfusion.[12 13] It may result from perfusion by extracorporeal pumps.[14]

The lack of circulating fibrinogen is not an isolated defect. Low platelet counts, and low levels of antihaemophilic globulin (factor VIII), Christmas factor (factor IX), and factor V are usually present at the same time.[7 15] This complex depletion of factors necessary for normal coagulation of the blood is, as would be expected, often associated with spontaneous haemorrhages, usually of capillary type, in the skin, and from the nose, mouth, and urinary tract, and severe post-partum uterine haemorrhage may occur. Unlike the majority of haemorrhagic diatheses, bleeding may follow venepuncture and blood may continue to ooze from the puncture for some time. In post-operative cases the bleeding is usually into the site of operation and not more widespread. Whether haemorrhage occurs or not, the patient is frequently severely shocked, and the clinical state may be complicated by subsequent oliguria and anuria as a result of renal damage.

It is now generally believed that the sequence of events leading to this complex syndrome is the result of the liberation into the circulating blood of tissue thromboplastin, which in turn produces intravascular coagulation and consequent formation of fibrin in the blood-stream.[1 6] This may occur where the tissue was destroyed, with accumulation of large amounts of fibrin in one place. Alternatively it has been suggested that small fibrin deposits may be formed in the blood-stream and so carried round the body, most being filtered out in the pulmonary circulation.[1 6] In contrast with this concept of intravascular coagulation, some authorities believe that fibrinolysis may be responsible for the syndrome.[16–19] The mechanism suggested is that a tissue kinase, acting as an activator of plasminogen, produces plasmin, which in turn, by proteolysis, digests the circulating fibrinogen and other coagulation factors, such as factors VIII and IX.[18 20] Certainly fibrinolytic activity can be detected in many cases of defibrination

1 Schneider, C. L., *Ann. N.Y. Acad. Sci.*, 1959, **75**, 634.
2 Barry, P. A., Geoghegan, F., and Shea, S. M., *Brit. med. J.*, 1955, **2**, 287.
3 Scott, J. S., ibid., 1955, **2**, 290.
4 Schneider, C. L., *Amer. Acad. Obstet. Gynec.*, 1953, **1**, 321.
5 Tuller, M. A., *Amer. J. Obstet. Gynec.*, 1957, **73**, 273.
6 Schneider, C. L., in *Progress in Haematology*, 1956, p. 202, New York.
7 Ingram, G. I. C., and Mann, C. V., *Thorax*, 1959, **14**, 236.
8 Mathey, J., Daumet, P., Soulier, J. P., Le Bolloch, A. G., and Fayet, H., *Mém. Acad. Chir.*, 1950, **76**, 977.
9 Penn, S. R., and Walker, J. H., *New Engl. J. Med.*, 1954, **250**, 764.
10 Marder, M., Weiner, M., Shulman, P., and Shapiro, S., *N.Y. St. J. Med.*, 1949, **49**, 1197.
11 Swan, H. T., Wood, K. F., and Daniel, O., *Brit. med. J.*, 1957, **1**, 495.
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13 Moore, J. M., *Brit. med. J.*, 1958, **2**, 1201.
14 Nilsson, I. M., and Swedberg, J., *Acta chir. scand.*, 1959, **117**, 47.
15 Sharp, A. A., Howie, B., Biggs, R., and Methuen, D. T., *Lancet*, 1958, **2**, 1309.
16 Albrechtson, O. K., Storm, O., and Trolle, D., *Acta haemat.* (*Basel*), 1955, **14**, 311.
17 Phillips, L. L., Montgomery, G., and Taylor, H. C., *Amer. J. Obstet. Gynec.*, 1957, **73**, 43.
18 Soulier, J. P., Alagille, D., and Larrieu, M. J., *Sem. Hôp. Paris*, 1956, **32**, 1.
19 —— Mathey, J., Le Bolloch, A. G., Daumet, P., and Fayet, H., *Rev. Hémat.*, 1952, **7**, 30.
20 Astrup, T., *Lancet*, 1956, **2**, 565.
21 Schneider, C. L., *Amer. J. Obstet. Gynec.*, 1955, **69**, 758.
22 Niewiarowski, S., and Kowalski, E., *Rev. Hémat.*, 1958, **13**, 320.
23 Schneider, C. L., *Amer. J. Obstet. Gynec.*, 1952, **64**, 141.
24 —— *Obstet. Gynec.*, 1954, **4**, 73.
25 Bierme, R., and Ducos, J., *Sang*, 1957, **28**, 673.
26 Sherry, S., Fletcher, A. P., and Alkjaersig, N., *Ann. intern. Med.*, 1959, **50**, 560.
27 Ratnoff, O. D., and Conley, C. L., *Bull. Johns Hopk. Hosp.*, 1951, **88**, 414.

syndrome, and it may be capable of augmenting the destruction of plasma factors started by the coagulation sequence, but it is doubtful whether it is ever the sole factor in the causation of this syndrome. In the majority of cases in which fibrinolytic activity can be detected it is only minimal, and it is unlikely that it could be detrimental to the host. However, if this activity becomes excessive, it may provoke a more disastrous loss of coagulation factors. The evidence suggests that, as fibrinogen depletion takes place, from whatever cause, there may be initially a qualitative alteration of the circulating fibrinogen which appears to make it unresponsive to the action of the thrombin.[15 27] This phenomenon may be due to an anticoagulant with heparin-like activity,[21] or alternatively partially lysed fibrinogen may act as an antithrombin.[22]

It is impossible to forecast in what circumstances the defibrination syndrome may develop in any given case, and prophylaxis is therefore impossible. The clinician can only bear it in mind when treating the sort of cases in which it is known to occur. The pathologist's task is to define its existence accurately and rapidly so that therapy may be instituted quickly. Many tests for this syndrome have been described, but observation of the whole-blood clotting-time and the type of clot formed have provided useful screening tests.[23] The reaction of the whole blood or plasma to the addition of thrombin is also reliable in providing a specific and speedy diagnosis.[3 15 23] Conventional biochemical estimations of fibrinogen are too time-consuming to be of value here.

The treatment of this syndrome lies in the rapid correction of the coagulation defect with concentrates of fibrinogen or reconstituted dried plasma, and the replacement of lost blood by whole blood or packed cells. In obstetric cases early evacuation of the uterus is the prime consideration, because defibrination may continue until this is done. It is debatable whether fibrinogen concentrates should be given immediately or withheld until after delivery. Some workers consider that, if therapy is started while the defibrination mechanism is active, the fibrinogen or plasma may provide material for continuing intravascular coagulation; so the patient may deteriorate further.[1 24] However, where immediate treatment with fibrinogen or plasma has been instituted before delivery no deleterious effects have been reported.

When the defect is severe or a spontaneous haemorrhagic state is established there is little alternative but to start treatment immediately. In the milder case, however, the decision on when to institute therapy must be carefully considered. If there is no haemorrhage and only a moderate plasma defect it would seem safe to delay therapy and await events. If this is done laboratory tests must be carried out at frequent intervals to detect any deterioration. To be effective, the initial dose of fibrinogen concentrate should be at least 6 g.; such doses can be administered in a volume of 600 ml., are non-toxic, and can be given in 30 minutes. If fibrinogen concentrates are not available, triple-strength plasma would seem to be the second choice, though much larger volumes of this preparation are necessary.[25]

Why concentrated fibrinogen has been found to be so effective in the treatment of the complex coagulation defect found in this syndrome remains a mystery, as whole blood and even plasma have not been so effective in restoring the coagulation mechanism to normal and arresting bleeding. In most cases the episode of defibrination is probably a once-and-for-all mechanism and immediate therapy should produce a rapid improvement, but occasionally very severe destruction of tissue may cause defibrination to continue and therapy may prove to be ineffective or even detrimental. What to do in these cases is a problem, but the logical therapy would seem to be the administration of heparin, a perhaps hazardous step when a haemorrhagic diathesis already exists. But the immediate risk of haemorrhage may be the least of the dangers in this event. These considerations do not apply to post-operative cases, when it is unlikely that any further tissue damage will follow the end of surgical intervention. Here immediate therapy is indicated to prevent dangerous internal haemorrhage. Steroids have been found to prevent haemorrhage after the intravenous administration of fibrinolysin activators in the treatment of thrombosis,[26] and they should be tried, especially when high fibrinolytic activity can be detected.

NATURAL CHILDBIRTH

Despite the increasing efficiency and diminishing hazards of obstetrical analgesic agents, the concept of painless labour without resort to drugs has caught the popular imagination. More and more pregnant women are seeking instruction on how to confound the literal biblical prophecy, "In pain thou shalt bring forth children."[1] Recently Dr. Roma N. Chamberlain has written an interesting study of "natural childbirth."[2] She points out that, while a few "unprepared" women suffer no pain at all in labour, many others are filled with fear not only of pain itself but also of drugs and especially of masks of analgesic apparatus. She proceeds to discuss the two main forms of preparation for childbirth. The "natural childbirth" propounded and publicized by the late Grantly Dick Read is based on a

concept of a vicious circle of fear–tension–pain.[3] This circle is to be broken by removing the fear by antenatal education, exercises, controlled breathing, physical relaxation, and constant companionship during labour. The Read method has been taken up not only in Great Britain but also in other English-speaking countries, including some centres in the U.S.A., notably Yale.[4] The Russian "psychoprophylactic method," on the other hand, is based on the belief that fear in labour is a Pavlovian conditioned reflex which can be removed by education and constant repetition that labour is painless. The woman can thus be conditioned to go through labour without drugs and without pain. This approach has been enthusiastically followed in France by F. Lamaze and his school, one of whom, P. Vellay, has written a book, now available in English translation,[5] detailing their present techniques. Stress is laid on instruction in physiology and anatomy, on controlled breathing and abdominal massage, and on constant repetition by all attendants that there is nothing to fear and that the method is always successful.

Dr. Chamberlain maintains that, while these two methods differ in rationale, they share much common ground, and that both blend with the technique of light hypnosis. Indeed, as she says, it is difficult to see exactly where education ceases and suggestion begins, and where suggestion ends and hypnosis begins. L. Chertok has reached the same conclusion.[6] The labels may differ but the formula is largely the same, a mixture of three interrelated analgesic factors—didactic, physiotherapeutic, and psychotherapeutic. He points out the difficulties which arise from our ignorance of the nature of labour pains and our lack of objective methods of measuring their severity. Further, he recalls that as recently as 1953 Lamaze and Vellay denied any real difference between the two methods. Vellay now says that the Read method offers the woman a passive role whereas psychoprophylaxis gives her an active one. A Frenchman has gone so far as to say that the Russian method is more acceptable to Frenchwomen because it appeals to the mind, whereas the British method appeals to the musculature.[7]

Both methods emphasize the importance of a consistently calm and confident attitude by all who come into professional contact with the pregnant woman. Old fears must be broken down and the success of new methods reiterated. Mental rather than muscular relaxation seems to be the key; yet O. S. Heyns has shown that artificial relaxation of the abdominal muscles by mechanical decompression shortens the duration and the pain of the first stage.[8] All this makes demands on the attendants, whether at home or in hospital, as well as on the patient. One sarcastic or questioning remark in labour can undo all the good instilled during pregnancy. The woman should not be left alone during her labour, and during the first stage the husband may be the most reassuring companion for her. As for the demand on the patient, "natural childbirth" is an unfortunate term because it suggests that under primitive conditions labour is quick and relatively painless, which is far from the case. Indeed, the modern techniques demand from the pregnant woman some education as well as intelligence.

Not all doctors are ready to concede that consistent advantages accrue from antenatal education and exercises. In one centre in Great Britain training for childbirth was not found to lessen the need, and the call, for pain-relieving drugs in labour.[9] On the other hand, those who teach the principles and the practical details of education for childbirth insist not only that analgesics are rarely required but that in addition the incidence of complications in labour is greatly reduced.[10] As to psychoprophylaxis, Wen-Chen in China claims 94% success[11]; others find no physical or obstetric advantage to the mother, though they admit she gains mentally.[12] With hypnosis ideal results are obtained in fewer than 10%, but the outcome is rated satisfactory in about 50%.[13] Perhaps C. L. Buxton put the matter in proper perspective when he asserted that programmes of preparation for childbirth are nothing more than the concentrated application of those basic humanitarian and obstetric principles which have been practised for generations.[14]

[1] Genesis, Ch. 3, v. 16.
[2] Chamberlain, R. N., *Monthly Bull. Minist. Hlth Lab. Serv.*, 1959, **18**, 190.
[3] Read, Dick G., *Childbirth Without Fear*, 1942, London.
[4] Thoms, H., and Wyatt, R. H. *Amer. J. publ. Hlth*, 1950, **40**, 787.
[5] Vellay, P., *Childbirth Without Pain*, 1959, London.
[6] Chertok, L., *Psychosomatic Methods in Painless Childbirth*, 1959, London.
[7] Lyonnet, R., *Lyon méd.*, 1956, **88**, 9.
[8] Heyns, O. S., *J. Obstet. Gynaec. Brit. Emp.*, 1959, **66**, 220.
[9] Rodway, H. E., ibid., 1957, **64**, 545.
[10] Heardman, H., *Physiotherapy in Obstetrics and Gynaecology*, 1959, Edinburgh and London.
[11] Wen-Chen, C., *Chin. med. J.*, 1957, **75**, 338.
[12] Winkelstein, L. B., *Amer. J. Obstet. Gynec.*, 1958, **76**, 152.
[13] Rochat, R. L., and Rossel, G., *Gynaecologia (Basel)*, 1957, **144**, 356.
[14] Buxton, C. L., *Penn. med. J.*, 1957, **60**, 171.

TEST OF PANCREATIC FUNCTION

When a patient suffers from steatorrhoea it is of cardinal importance to be able to recognize the disease which is causing it. One major cause of steatorrhoea is pancreatic disease, such as chronic pancreatitis, associated with poor secretion of pancreatic enzymes into the intestine. Two hormones liberated from the upper small intestine influence the secretory activity of the pancreas. Secretin (which was the first hormone ever to be discovered) causes the normal pancreas to secrete a large volume of juice rich in sodium bicarbonate. Pancreozymin causes the normal pancreas to secrete a juice rich in pancreatic enzymes. Both these hormones are now available as commercial preparations, and they constitute the basis of a test of pancreatic function described by I. N. Marks and S. L. Tompsett.[1] By passing a tube into the upper small intestine (and another tube into the stomach for the removal of gastric juice which would otherwise interfere with the test) the contents of the upper small intestine are collected after injection of secretin and pancreozymin, and measurements are made of the volume, bicarbonate content, and amylase content. No additional diagnostic information comes from measuring the amount of trypsin and lipase. In cases of pancreatic disease in which the external secretions are diminished all three

[1] Marks, I. N., and Tompsett, S. L., *Quart. J. Med.*, 1958, **27**, 431.
[2] Jorpes, J. E., and Mutt, V., *Gastroenterology*, 1959, **36**, 377.

of these measurements give low values compared with those of healthy subjects. The earliest sign of pancreatic secretory hypofunction appears to be a drop in the amylase content of the pancreatic juice. The original article should be consulted for the precise details. The pancreozymin preparation contains some cholecystokinin, which causes contraction of the gall-bladder. It has therefore also been used as a test of gall-bladder function[2] in place of a fatty meal for cholecystography.

NATIONAL ACCIDENT SERVICE

A thorough attempt to improve the services for treating accidents throughout Great Britain and Ireland is now under way. Last November the president of the British Orthopaedic Association, Mr. H. J. Seddon, communicated with representatives of different branches of the profession with the idea of holding a conference to discuss how the treatment of the growing numbers of patients with injuries from accident could be improved. As was said at the time in these columns, "all branches of clinical medicine are concerned in the prevention and treatment of all types of accidents."[3] The conference met early this year, and a widely representative committee has been set up to study the question. This Accident Services Review Committee has for its chairman Mr. H. Osmond-Clarke, of London, and its vice-chairman Mr. Walpole Lewin, of Oxford. A list of members so far appointed is published elsewhere.[4]

The task before the committee is to find out how different types of medical men see the problem—neurosurgeon, thoracic surgeon, orthopaedic surgeon, general practitioner (in town and country, in highlands and lowlands)—and then to prepare a report. The diversity of views that may be expected, many of them critical, was foreshadowed in the discussion on accidents held at the B.M.A. Annual Meeting in Birmingham two years ago.[5] It is hoped that the organizations represented on the committee will send in memoranda so that these can be considered alongside the report of the British Orthopaedic Association,[6] published last autumn. The final recommendations would then be discussed with the Minister of Health through the usual negotiating machinery of the profession. The committee intends to provide a continuing review of the accident services and to concern itself only with, in a general sense, the treatment of patients, not with terms and conditions of service.

The formation of this committee will be welcomed throughout the medical profession. Just a quarter of a century has passed since the report of the B.M.A. Committee on Fractures was published.[7] Its call for an "organized fracture service" (which would not be literally confined to the treatment of fractures) was repeated in later reports. It is time something was done, and this new committee has a great opportunity to see that it is.

[3] *Brit. med. J.*, 1959, **2**, 1009.
[4] See *Journal*, p. 816, and *Supplement*, p. 112.
[5] Ibid., 1958, **2**, 304.
[6] British Orthopaedic Association, *Memorandum on Accident Services*, 1995.
[7] *Brit. med. J. Suppl.*, 1935, **1**, 53.

INFECTIOUS DISEASES IN SCHOOLS

Fifty years ago it was common when a case of infectious disease occurred for all other children in the household to be excluded from school for the duration of the incubation period. The great loss of time at school resulting from this, coupled with a growing realization that exclusion of contacts from school did not affect the development of epidemics of the common infectious diseases, led to a gradual relaxation of these restrictions. Reduction in clinical severity of some of the infectious fevers has made restrictive measures even more difficult to justify than formerly.

In Great Britain practice is based on the memorandum issued by the Ministries of Education and Health.[1] This memorandum rejects the policy of automatic exclusion from school of all contacts, but sees some virtue in selective exclusion—for example, children living in a heavily infected street or district, or the contacts of first cases, though exclusion later when the disease is widespread might be of comparatively little value. An appendix gives suggested exclusion periods for patients and contacts of certain diseases. It is the opinion of both Ministries that the rules governing the exclusion of contacts should not be more rigid than those suggested. No exclusion is recommended for contacts of scarlet fever, German measles, mumps, and chicken-pox; for measles exclusion is limited to susceptible contacts under 5 years of age, and for whooping-cough susceptible contacts under 7, while exclusion of contacts is recommended for diphtheria, poliomyelitis, encephalitis, and meningococcal infection. Most of the local authorities base their practice on this memorandum. Differences between areas are inevitable, and not by any means due to reluctance to march with the times, for the memorandum recognizes that the outlook may be altered by local conditions.

A new publication from the World Health Organization surveys the legislation on communicable diseases in schools in a number of different countries.[2] A comparison is made with another report in 1952,[3] and it is noted that in recent years there has been a tendency to lessen the stringency of exclusion measures for both patients and contacts. The most extraordinary feature of the report is the complete lack of uniformity in the measures imposed in different countries in spite of the fact that much of the basic information on which the measures are based is common ground. For example, while in Great Britain and in the United States (New York City) contacts of scarlet fever are not excluded from school, other countries impose periods of exclusion of 5, 7, 8, 12, 14, or 42 days. These periods may be varied by circumstances, such as whether or not the patient is removed to hospital or whether penicillin has been administered.

The World Health Organization has done well to bring to light the wide variations in practice throughout

[1] *Memorandum on the Closure of Schools and Exclusion from School on Account of Infectious Illness*, Ministry of Education and Ministry of Health, 1956. H.M.S.O.
[2] *Communicable Diseases in Schools*, 1959. World Health Organization, Geneva.
[3] *International Digest of Health Legislation*, 1952, **4**, 169.

the world. One point on which there is fairly general agreement is that school closure should seldom be necessary. In country districts where a central school takes pupils from a number of villages, some of which have cases of poliomyelitis, the arguments for closure of the school or mass exclusion of pupils from infected villages may be compelling, but such action will only rarely be justified in towns.

INFECTIVE CHOLANGITIS AND CHARCOT'S BILIARY FEVER

Infection of the biliary tree is almost always secondary to obstruction to major bile-ducts, usually owing to gall-stones or to post-operative biliary stricture. The responsible organism is commonly the Gram-negative *Escherichia coli*, though mixed infections are not unusual. The classical triad of symptoms is jaundice, pain in the right upper quadrant of the abdomen, and chills and fever (Charcot's intermittent biliary fever).[1] At the height of the fever there is a septicaemia due to Gram-negative organisms, which can often be cultured from the blood and urine.

The severity of the clinical picture is very variable. The most serious type is described by B. M. Reynolds and E. L. Dargan[2] as "acute obstructive cholangitis." In addition to the classical symptoms their patients showed lethargy or mental confusion and a severe degree of shock. This was believed to be due to overwhelming sepsis and to the accumulation of purulent material under increasing pressure in the biliary tract. In the five patients described the obstruction was due to stones in the common bile-duct. The first patient's condition seemed too precarious to warrant surgical intervention and death followed; necropsy showed the features of *E. coli* septicaemia. After this experience the next four patients were operated upon and the biliary obstruction relieved. Three survived, the other dying on the 22nd day after operation; post-mortem examination showed a myocardial infarct and multiple liver abscesses. Despite the apparently moribund condition of these patients, response to emergency decompression of the common bile-duct is so dramatic that operative intervention is mandatory.

Another aspect of the problem is described by F. M. Howard and his colleagues[3] from the Mayo Clinic. Their six patients suffered from choledocholithiasis, presenting with fever but without jaundice and in four without pain. Charcot in his original description in 1877 described one patient without jaundice. Osler,[4] in 1890, emphasizing the importance of irregular pyrexia of short duration, had not seen a non-icteric victim of the syndrome. Howard and co-workers noted that, though the patients were not clinically jaundiced, measurement of the proportions of conjugated and unconjugated bilirubin in the serum might be helpful, for four of their six patients showed a slight rise in the level of the conjugated bilirubin. Intravenous cholangiography may also be useful. It is important to consider obstruction to the common bile-duct in any patient with recurring attacks of fever. Surgical exploration may be the only method of confirming or denying the possibility of Charcot's fever in some patients.

[1] Charcot, J. M., *Leçons sur les maladies du foie, des voies biliares et des reins, faites à la Faculté de Médecine de Paris*, 1877, Paris.
[2] Reynolds, B. M., and Dargan, E. L., *Ann. Surg.*, 1959, **150**, 299.
[3] Howard, F. M., Jr., Martin, W. J., Stauffer, M. H., and Hallenbeck, G. A., *Arch. intern. Med.*, 1959, **103**, 565.
[4] Osler, W., *Johns Hopk. Hosp. Rep.*, 1890–1891, **2**, 3.

SOCIAL AND PREVENTIVE MEDICINE

There is usually something of interest to be learned about the teaching of social and preventive medicine in the annual reports of the London School of Hygiene and Tropical Medicine. The most recent of these[1] describes the investigations and conclusions of a number of study groups set up by the D.P.H. class. One group, for instance, tried to find out whether the children of mothers who went out to work suffered because of this. The problem proved a difficult one, but the limited information obtained suggested "that it is not easy to demonstrate that children are adversely affected by the mere fact that their mothers work." Another group continued an investigation begun by the previous year's class into the smoking habits of schoolchildren and found that at every age (over 14) more boys were smoking than was found a year earlier. The influence of friends was the main impetus in starting to smoke, and for the most part it appeared that the boys had little opposition to face from their parents. Perhaps the most original of the subjects set for study was an assessment of the amount of social work undertaken by the police. It was a novel conception to members of this group who came from overseas that "the police were looked upon as advisers whose help was sought in almost any problem ranging from lost canaries to marital arguments." Much of the work of the police was found to stem from medico-social problems—for instance, homosexuality, prostitution, aggressive behaviour, truancy, and so on. The police and social workers both emphasized that discharged prisoners and patients recently discharged from mental hospitals gave rise to many of their problems.

Another interesting finding described in the report was that of the Department of Human Nutrition, which was asked to investigate the dietaries of a number of hospitals in West Cornwall. Having found that the structure of the dietaries was faulty and that "plate-waste" was sometimes excessively high, the department concluded that because of the difficulties inherent in hospital catering it was doubtful if the best of existing arrangements in Britain would ever be entirely satisfactory from both catering and nutritional points of view. Rather than provide an individual service for each hospital, it might be better, the report states, to use modern equipment and techniques to prepare varied meals in centres and then to hold them in deep-freeze until shortly before they were to be served to the patients. The meals could be quickly heated in a ward "galley" and served in the manner now customarily practised in air-liners.

[1] London School of Hygiene and Tropical Medicine. *Report on the Work of the School for the Year 1958-1959.*

Drug Treatment of Disease

PAEDIATRIC PRESCRIBING

BY

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The whole attitude to prescribing has changed in recent years and in paediatrics perhaps more than in general medicine, because mothers no longer *expect* the doctor to prescribe a bottle of medicine (unless it contains an antibiotic), and treatment is much more specific and less empirical. For example, mercury-containing teething powders, grey powders (hydrarg. cum. cret.), and laxatives as first choice routinely are things of the past, and most doctors to-day realize that children's coughs are more often the result of upper respiratory infection than indicative of bronchitis and require neither stimulant nor sedative expectorant mixtures, and that tuberculosis seldom causes chronic cough in childhood.

As diagnosis has become more exact and treatment more specific, so have more potent drugs been made available, necessitating greater care in prescribing and an ever-present look-out for untoward side-effects. The old methods of grading the dose according to the child's age or the infant's weight are no longer generally applicable. Each drug and each child must be considered separately. Children are unusually tolerant of some drugs—for example, isoniazid, amphetamine, and antihistaminics—and may need the same dose as an adult: others, such as morphine, should be prescribed only after most careful consideration and in strictly limited dosage which should not exceed 0.1 mg./lb. (1/600 gr./lb. or 0.2 mg./kg.). Pethidine, which is so valuable as an antispasmodic and sedative in such emergencies as laryngitis stridulosa (false croup), may be given by injection in a dose of 0.5 mg./lb. (0.1 mg./kg.).

Whenever possible treatment by mouth should be prescribed—in form and volume suitable for the age of the patient. But, when rapidity of action is urgent, parenteral administration is essential, as it is also if vomiting is a feature. When injections are necessary they should be given in small volume, preferably not exceeding 1 ml., and as infrequently as possible.

As there is no "golden rule" for estimating dosage in infancy and childhood, some of the more common conditions encountered will be discussed to illustrate the principles involved: acute infections requiring antibiotics, allergy, rheumatism, and tuberculosis (prophylactic and therapeutic), anaemia, and recurrent convulsions.

INFECTIOUS DISEASES

Acute Infections

The acute infections of non-viral origin include pneumonia, tonsillitis, otitis, enteritis, meningitis, cellulitis and osteomyelitis. Though all of these infections may on occasions be caused by viruses, only the bacterial ones will be considered, because there is as yet no general virucidal drug available. The drugs which are likely to be helpful are penicillin, sulphonamides, chloramphenicol, the tetracyclines, erythromycin, and neomycin for enteritis.

The chief points to be considered are the drug of choice, determination of the optimal quantity and the minimal duration of treatment, complications, the value of mixing antibiotics unless they have clearly been shown to be synergistic—which is very rare: they are often additive (which offers no special advantage) but may sometimes be antagonistic (for example, penicillin and tetracyclines).

Choice of Drug

This will be dictated by the site of infection and the most likely infecting organism. Pneumonia in a child is likely to be pneumococcal and to respond to penicillin or sulphonamides. Meningitis may be assumed, in the first instance, to be meningococcal if the patient is over the age of a year and there is no history of previous otorrhoea, and the same two drugs would be indicated. The severity of these infections and the different modes of action of the sulphonamides (bacteriostatic) and penicillin (bactericidal) justify their combination. Although either alone may prove successful it is wiser to give both together in infants suffering from meningitis, and, indeed, in severe pneumonia—the penicillin by intramuscular injection and the sulphonamide by mouth.

The tendency is to give larger doses of penicillin than formerly, and it is indeed fortunate that its rapidity of excretion precludes any severe toxic effects. 1–2 million units would be a suitable dose at any age in childhood. The dose of sulphonamide is from 1 g. at 1 year to 2 g. at 5 years and 3 g. at 10 years of age. One dose of this combination (i.e., one intramuscular injection of penicillin and one oral dose of sulphonamide), given as soon as the diagnosis is made, is sufficient to effect a cure in the majority of children with lobar pneumonia or meningococcal meningitis, and is the safest method available.

Failure of response suggests that some other organism than the pneumococcus or the meningococcus is responsible for the respective infections. In the case of meningitis this may be confirmed by examination of the cerebrospinal fluid, and subsequent treatment will be modified accordingly. In a child with pneumonia, failure to improve within 24 hours (improvement being judged by the over-all general condition, fall in temperature and diminution in toxaemia but not with any remarkable change in auscultatory signs) would likewise be an indication for changing the therapy. Unfortunately, only these two specific conditions can be relied on to respond consistently to this "stosstherapy," and, though pneumococcal meningitis will respond to the same combination of drugs, several doses—at intervals of 24 hours—are likely to be necessary before complete recovery. There is, however, no need for repeated doses at shorter intervals, and the decision whether further treatment is necessary, or whether it should be changed, can be made at the daily visit.

In infancy bronchopneumonia is likely to be staphylococcal and meningitis may be due to *H. influenzae*; in the newborn *Escherichia coli* may be implicated. In none of these would penicillin be first choice, nor could stoss-therapy be used. Streptomycin is particularly valuable in infections in the newborn, and may be given for not more than three days in doses of 125 mg. 12-hourly by intramuscular injection. It would be hoped that before three days had passed the infective organism might have been determined and its antibiotic sensitivities known; if further treatment were necessary, change should be made to the appropriate oral antibiotic. For bronchopneumonia due to *H. influenzae* or *Bordetella pertussis* in infancy chloramphenicol, 125 mg. 3-hourly or 4-hourly for 48–72 hours, will be found most valuable. This dosage should not be continued for longer periods. It should be reduced to thrice daily, and if, after three or four days on this reduced dose, further treatment is indicated it is wiser to change to chlortetracycline (see under "Complications").

Osteomyelitis is usually staphylococcal, and cellulitis may be streptococcal or staphylococcal. Penicillin 1–2 million units twice daily should produce distinct improvement after 24 hours both generally and locally, if the organism is sensitive. Should there be no, or inadequate, improvement after 48 hours, the antibiotic should be changed rather than the dose of penicillin increased, for it is probable that the organism will be found to be resistant. After the initial parenteral treatment and clinical improvement oral therapy may be substituted. For osteomyelitis treatment will have to be continued for at least three weeks, perhaps longer. For tonsillitis and otitis penicillin would again be first choice, and a similar procedure of initial injection followed by oral treatment is recommended. It is particularly important in children of school age with tonsillitis which proves to be streptococcal that penicillin treatment should be continued for at least 10 days; this method is the best at present known to minimize the risk of rheumatism.

Large Doses for Short Time

It will be seen from the foregoing that the important principle of chemotherapy in the treatment of infants and children with acute infections is to give large doses—and the more severe the infection the larger the dose—for a short time, each dose being ordered selectively. In such circumstances the amount of the drug is of secondary importance; only with continued therapy are complications likely. The dose of penicillin may be virtually unlimited, though it will seldom be necessary to exceed 4 million units in 24 hours. Crystalline penicillin G (benzyl penicillin) may be used for intramuscular injection, and the potassium salt of phenoxymethyl penicillin (potassium penicillin V) is recommended for oral use.

Chloramphenicol and the tetracyclines may be given in doses of 25–50 mg./lb./day (50–100 mg./kg.) divided into four or six doses according to the severity of the infection. Erythromycin has a similar field of activity to that of penicillin and is most properly reserved for the treatment of infections with organisms which are penicillin-resistant. Dosage is the same as for the tetracyclines. Neomycin is of particular value in the treatment of enteritis. The dose is 25 mg./lb./day (50 mg./kg.). Because of its liability to be followed by thrush it is often given in combination with an antimonilial agent such as nystatin, 250,000 units daily in infancy, and 500,000 units daily for children.

Complications

If antibiotic treatment has to be continued for more than three days the effects of the resultant alteration in the intestinal flora must be considered, together with the risk of thrush. The tetracyclines may cause stomatitis and perianal dermatitis; penicillin sensitivity, which is uncommon, may result in dermatitis. Chloramphenicol may—very rarely—produce aplastic anaemia; it is wise, therefore, to give it for a short period only; probably a maximum of seven days should be set. It is true that a blood dyscrasia may arise before this time, but this is extremely rare and most unlikely, and chloramphenicol is such a valuable drug that this is a risk which may fairly be taken. Streptomycin, and particularly dihydrostreptomycin, earned an unenviable reputation for toxic effects on the auditory nerve, and the former also for its effects on the vestibular nerve. In the treatment of acute infections (now being considered), dihydrostreptomycin would not be used, and streptomycin is not toxic in infancy if given only for a few days.

Combined Therapy

This is not recommended unless specifically indicated. A mixture of sulphonamides ("sulphatriad") is justified because there is evidence that this reduces the risk of renal complications. Severe infections, such as meningitis, and subacute bacterial endocarditis (which is rare in childhood) are special indications. In prolonged therapy, as, for example, in tuberculosis, combined therapy is customary in adults to reduce the liability to the appearance of resistant strains, but, in view of the efficacy of isoniazid in the treatment of childhood tuberculosis, this drug may well be used alone in the treatment of primary infections. In the severe postprimary manifestations, such as meningitis and miliary spread, it is obviously wiser to combine streptomycin and isoniazid or isoniazid and P.A.S.—just as more than one drug is recommended in the treatment of such severe infections as meningitis or pneumonia. Isoniazid is likely to fail only if the child being treated has been infected primarily with an isoniazid-resistant organism. Resistance is unlikely to develop during isoniazid treatment if the initial infection has been (as is usually the case) with a sensitive organism.

Prophylactic Treatment

The conditions which in childhood call particularly for continued prophylaxis are rheumatism, mucoviscidosis, and perhaps tuberculosis.

Rheumatism.—Penicillin has now completely replaced sulphonamides. The only complication encountered has been drug sensitivity. This usually necessitates complete and permanent avoidance of penicillin and penicillin-containing drugs or injections.

Mucoviscidosis (fibrocystic disease of the pancreas).—The prevention of pulmonary infections in children with this disease has been the major factor in prolongation of life. Chlortetracycline has proved most valuable, but repeated checks on the bacterial flora of the respiratory tract are necessary, and the antibiotic may have to be changed from time to time.

Tuberculosis. — The long-term administration of isoniazid is at present being investigated in the U.S.A. Isoniazid is a well-tolerated and non-toxic drug during childhood, and doses up to 10 mg./lb./day (20 mg./kg.) may safely be given for many months. This provides a therapeutic level; from 2 to 5 mg./lb./day (4–10 mg./kg.) would probably be adequate for prophylaxis. There is no evidence that pyridoxine deficiency occurs in children having isoniazid, even for prolonged periods, nor does the drug alter the intestinal flora.

ALLERGY

The management of the allergic child involves both specific and non-specific therapy. In the latter the antihistaminic drugs have proved of great value in many cases. The principle here is to give the maximal tolerated dose for a long period of time. There are many antihistaminics, and some children respond to one and not to others; trial should therefore be made of alternatives if the first is not successful. The maximal dose at any age is determined first by the development of nausea, vomiting, or undue sleepiness, and then maintaining the dose at just below this toxic level. If, for example, pyramine maleate ("anthisan") is being used, 0.1 g. is given *with* each meal (this minimizes the occurrence of nausea) and increased by 0.1 g. daily. For example:

Breakfast	Dinner	Tea	Supper
1	1	1	1
2	1	1	1
2	2	1	1
2	2	2	1
2	2	2	2
3	2	2	2

and so on to maximal tolerance—which is then maintained. It is singularly unsatisfactory to prescribe a fixed estimated dose for any child. If the required dose involves the ingestion of more than 8 tablets a day it is then preferable to prescribe a stronger drug—for example, promethazine ("phenergan").

ANAEMIA

For the common nutritional anaemia ferrous sulphate is the preparation of choice, and may be given in an acid mixture or in tablet form according to the age of the child. In infancy it is usually well tolerated, but, for children too young to swallow tablets and whose digestion is upset by ferrous sulphate, an iron chelate solution such as ferrous aminoacetosulphate ("plesmet") is recommended. Whatever form of iron is used, good results are unlikely in the presence of infection; this should always be treated first. Lack of response to treatment in an undoubted case of iron-deficiency anaemia should lead to a search for the focus of infection.

RECURRENT CONVULSIONS

Individual children react differently to different antiepileptic drugs, as they do to the antihistaminics, and it may be only by the method of trial and error that the most effective one is determined. With due regard to the toxic side-effects of the particular drug, it may be said that the dose required is the smallest that will effectively control the incidence of the convulsions. This may vary widely from patient to patient—even of the same weight and age. Because long-continued treatment is inevitable, special watch must constantly be kept for the appearance of toxic effects.

Reports of Societies

CHEMOTHERAPY OF LEPROSY

[FROM A SPECIAL CORRESPONDENT]

At a meeting of the Royal Society of Tropical Medicine and Hygiene on February 18 Dr. T. F. DAVEY, formerly director of the Leprosy Service Research Unit, Uzuakoli, Eastern Nigeria, presented a paper on "Some Recent Chemotherapeutic Work in Leprosy," including a discussion of problems involved in clinical trials.

Diaminodiphenyl sulphone (D.D.S.), Dr. Davey stated, was now accepted as the standard treatment of leprosy because of its effectiveness, simplicity of administration, and low cost. There was no unequivocal evidence of drug resistance with D.D.S. Nevertheless, alternative or more active drugs were needed to avoid hypersensitivity and reaction or reduce the long period of treatment. In their search for new drugs workers on leprosy owed a great debt to their colleagues in the field of tuberculosis, because all anti-leprosy drugs now in common use were first studied in relation to tuberculosis. In addition, the methods developed for controlled trials of new drugs in tuberculosis had drawn attention to the need for similar care in leprosy. These methods, however, were more difficult to apply to leprosy than to tuberculosis.

Trials of New Drugs

Ideally, drug trials should be carried out on patients with diffuse lepromatous leprosy. The widespread use of D.D.S. had reduced the number of these cases and less severe lepromatous diseases had had to be included. It was important to exclude the dimorphous type of cases, which clinically might be mistaken for less severe lepromatous leprosy, because they responded more readily to chemotherapy. The two types could be distinguished histologically. No patients who had received previous treatment should be included.

Without the means of culturing leprosy bacilli bacteriological assessment depended on determining the number of bacilli in smears or histological sections from lesions. Bacteriological assessment was the most important measure of chemotherapeutic response, but unfortunately the available methods were crude and the numbers of bacilli varied considerably from lesion to lesion in the same patient. Variables could be diminished by adopting standard methods —using a bacterial index—and sampling from several different sites. Furthermore the proportion of stained bacilli (by the Ziehl-Neelsen method) showing granular forms increased in patients responding to chemotherapy and Dr. Davey had added this criterion to his bacteriological assessment. Histological examination was also valuable, not only for confirming the type of leprosy, but also for assessing healing and the number of bacilli. Because of scarcity of suitable cases for chemotherapeutic trials Dr. Davey had compared the bacteriological response (plotted as bacterial index) to a new drug with the average response obtained from accumulated experience in a large number of cases receiving D.D.S.

"Ciba 1906" and "Etisul"

A thiourea derivative, "Ciba 1906," had been extensively studied at Uzuakoli and found to be as active or slightly more active than D.D.S. Administered daily, by mouth, in doses up to 3 g. it produced no drug toxicity or leprosy reactions. Recently in the prolonged trials of patients on Ciba 1906 alone evidence of drug resistance had appeared between the 36th and 44th months. Ciba 1906 alone should, therefore, not be given beyond two years. It was the drug of

choice in patients hypersensitive to D.D.S. The late outcome of trials of Ciba 1906 in combination with D.D.S. was now being studied.

Recent trials of the new drug "etisul" (diethyl dithiolisophthalate) had shown definite and often powerful therapeutic activity in some of the patients. Treatment by inunction had resulted in no toxicity, and the unpleasant smell (of garlic) could be masked by a perfume. With etisul alone significant improvement, definitely greater than with D.D.S., was observed by the third or fourth month, but evidence of drug resistance then appeared. Current trials suggested that in combination with D.D.S. or Ciba 1906 improvement could be maintained for six months or more and that the improvement was greater than that obtained with D.D.S. or Ciba 1906 alone.

Discussion

Dr. R. J. W. REES (London) opened the discussion by stressing the importance of maintaining centres for conducting therapeutic trials in leprosy. He suggested that some of the methods used for tuberculosis trials might be applied with advantage in leprosy, and severely criticized the use of retrospect comparisons. Recent studies, carried out with Dr. R. C. Valentine, had shown that granular stained leprosy bacilli examined in the electron microscope show morphological changes similar to those seen in dead mycobacteria or *Escherichia coli*.

Dr. G. W. DRIVER (Manchester) described the experimental background to etisul carried out by I.C.I. Activity was probably due to the release of ethyl mercaptan, which required an intracellular (monocyte) environment for optimum effect. Dr. W. H. JOPLING (London) discussed the results of therapeutic trials with etisul and "vadrine" alone and in combination with D.D.S. He drew attention to the severe pain (nerve, bone, and joint) experienced by leprosy patients.

Dr. D. J. RIDLEY (London) described the semi-quantitative method he had developed for determining the bacterial index from serial biopsies in histological sections and its successful application for assessing drug activity. Dr. K. R. CHATTERJEE (Calcutta) reported his experience with Ciba 1906 and etisul and the criteria used for assessing drugs in India. Dr. UTKO (Ankara) briefly referred to the leprosy campaign in Turkey.

ROLE OF INHERITANCE IN DISEASE

LIVERPOOL MEDICAL INSTITUTION SYMPOSIUM

At an ordinary meeting on February 18 the Liverpool Medical Institution discussed "The Role of Inheritance in Common Diseases." The diseases considered included peptic ulcer, rhesus-sensitization, goitre, rheumatic disease, and tuberculosis.

Introducing the symposium, Dr. C. A. CLARKE said that for many years it had been realized that common diseases of obscure aetiology were due to a combination of factors, environmental and inherited, and the proportion of each might vary greatly in the individual. In the past the "soil," although given due emphasis, was passed off under such terms as the "constitution" or "diathesis" of the patient. Later there was some advance in that certain diseases were thought to be associated with other bodily or mental characteristics. Thus, early greying of the hair was thought to predispose to Addisonian anaemia, asthmatics were considered usually to be of dark colouring, and in duodenal ulcer various psychological types and certain physical traits were thought to predispose to the disease. However, these were not discrete but graded characters, and were quite useless for assessing associations precisely.

Recently, much more accurate genetic markers had been discovered—for instance, the blood groups, the ability to taste phenylthiocarbamide (P.T.C.), secretion of the blood-group substances in the body fluids, and the presence of protein groups such as the haptoglobins. Essentially with all these a person was either one thing or the other, and only rarely intermediate. Some of these markers were undoubtedly associated with certain diseases, although the associations were often small.

Liability to Peptic Ulcer

Dr. R. B. MCCONNELL said the foundation for the recent advances was laid in 1951, when it was demonstrated conclusively that heredity played a part in both duodenal and gastric ulcer, and that the high familial incidence could not be due entirely to members of a family having a common environment. The familial pattern of inheritance would fit in with a polygenic inheritance and recent research had been directed to finding out which genes were concerned. We now knew the identity of two of the genetic loci concerned in duodenal ulcer. Group-O people were about 35% more liable than those of the other groups, and non-secretors were about 40% more liable than secretors. If we took the least susceptible people—the secretors of A, B, and AB—as a baseline, there was an increasing order of liability with the group O non-secretors, the most susceptible type, about 2½ times more liable. If it were not for the O gene and the non-secretor gene, there would be 20% fewer ulcer patients than at present.

We did not know yet how these genes caused this differential liability. The most likely explanation was that they were concerned in the tissue resistance of the duodenum, and that an immunological mechanism was involved.

Protection against Erythroblastosis

Dr. RONALD FINN pointed out that only about one in 20 rhesus-negative women married to a rhesus-positive husband became sensitized to the rhesus factor. Thus there were probably protective mechanisms for the other 19 matings. Levine himself had been the first to suggest the hypothesis that ABO incompatibility was protective against erythroblastosis foetalis. In a series of 164 families with erythroblastosis they had found that the percentage of ABO-incompatible matings was reduced to 24%, and that the immunizing foetus (when its status could be exactly determined) was always compatible. Using a modification of the Zipursky method for detecting foetal red cells, they had also investigated the blood of 50 mothers within 72 hours of delivery. Foetal cells were found in about one-third of the compatible matings, but were never found in incompatible matings. This gave further support to the hypothesis that ABO incompatibility was protective.

Hereditary Factors in Thyroid Disease

Conventional genetic studies had shown, said Dr. F. D. KITCHIN, a more or less conclusive mode of inheritance in toxic diffuse goitre and in the rarer conditions of familial goitrous cretinism, congenital deafness with goitre, and athyreotic cretinism. In simple goitre the results of pedigree studies had been conflicting since genetic effects were often overwhelmed by environmental factors. With Dr. Howel Evans he had used the gene marker of the P.T.C. taster response to study 447 patients with thyroid disease who had had thyroidectomy and in whom the gland had been examined histologically. They found that the taster/non-taster genotypes were important in determining the type of thyroid disease an individual developed. In the group with diffuse toxic goitre there was a highly significant deficiency of non-tasters (16.6%), while in the group with multiple adenomata there was a significant excess of non-tasters, more marked among the men (64.4%) than the women (36.2%). Perhaps these findings could be explained on the basis of a differential susceptibility to naturally occurring goitrogens (of the thiocarbamide class) in cow's milk.

Rheumatic Diseases

In rheumatic fever environmental factors were undoubtedly predominant, said Dr. J. C. WOODROW. Infection with group A haemolytic streptococci was essential and poor environmental conditions strongly conduced to the disease. However, host factors must play some part in the individual case because even under optimal environmental conditions a low incidence of disease was noted. Familial aggregation, in part genetic, had repeatedly been demonstrated. On the supposition that the pathogenicity of the haemolytic streptococcus in the pharynx might be influenced in some degree by the presence or absence of particular, locally secreted, blood-group substances, the incidence of the latter in patients with rheumatic fever had been investigated. Some combined figures from Liverpool and Taplow showed a significant rise in the percentage of non-secretors of A, B, and H substances which was being further examined. Moreover, among those patients who had had rheumatic fever there was a significant deficiency of group O subjects. Attempts were being made to grow the haemolytic streptococcus on media with and without A, B, and H blood-group substances to find out whether this made any difference.

In rheumatoid arthritis no constant environmental factor was known, but a similar familial aggregation suggested the operation of a genetic factor. A serum factor was present in most, if not all, cases of rheumatoid arthritis, and this was believed to be intimately connected with the pathogenesis of the disease. Family studies have shown a significantly high incidence of positive tests for this factor in the relatives of patients with arthritis when compared with controls.

Response to Antituberculous Therapy

Dr. D. A. PRICE EVANS said that variations in susceptibility to communicable disease, and variations in response to treatment, had intrigued physicians for years. Recent work on the metabolism of isoniazid had shed some light on a facet of this problem. The concentration of isoniazid in the plasma had been determined chemically six hours after ingestion in 484 subjects, and the resulting frequency-distribution curve was bimodal. Individuals were divided by the antimode into rapid or slow inactivators of the drug. There was no heterogeneity for these characters due to sex or age, and on the numbers studied the distribution of phenotypes appeared to be the same in American Negroes as in "whites"; 267 of the subjects constituted 53 "white" families. The family data were consistent with the hypothesis that the character for slow inactivation was recessive. A "dosage" effect of the allele controlling the dominant character was also demonstrable in that there was a significant difference between the mean concentration of plasma isoniazid in recognizable heterozygotes and the mean value in all other "rapid-inactivator" family members.

Natural Selection in Man

Dr. P. M. SHEPPARD wound up the symposium with some thoughts on natural selection in man. The data had shown that certain inherited traits, such as the ABO blood-groups, secretor status, and P.T.C. taste-response, were associated with some common diseases in such a way as to suggest that the genes responsible for the traits were also affecting susceptibility to the disease in question. It had long been known that two or more forms of a gene could not remain common in a population except under highly specific conditions of opposing selective forces. And, since there were two or more forms of a gene responsible for each of the nine major blood-group systems, as well as for the secretor and P.T.C. taste-response characters, these special opposing selective forces must be acting as Ford had predicted in 1945. These predictions had now been confirmed. However, the diseases concerned were chiefly ones of middle or old age, and therefore did not much reduce fecundity. Consequently it was safe to predict that other and more powerful effects of these genes were yet to be found.

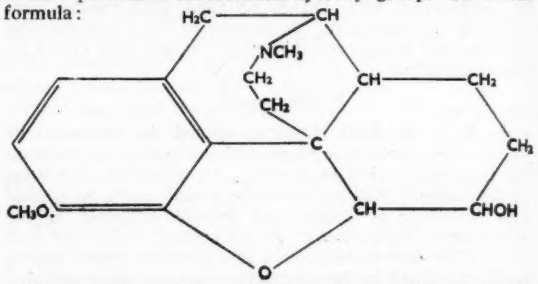
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Dihydrocodeine

"DF 118" (Duncan, Flockhart).

Chemistry.—Codeine is converted to dihydrocodeine by catalytic hydrogenation, which removes the double bond in the α-position to the alcoholic hydroxyl group. Structural formula:



Pharmacology.—Like codeine, dihydrocodeine initially causes depression of the central nervous system in mice and rabbits but in smaller doses. Reflex activity is augmented, though less than with the same dose of codeine. The analgesic, respiratory, and constipating effects of dihydrocodeine in cats and rabbits are greater than those of codeine. In man 30 mg. of dihydrocodeine is about as analgesic as 10 mg. of morphine but produces less respiratory depression, dizziness, and nausea. A comparison with pethidine showed that dihydrocodeine depresses respiration less in (analgesically) equipotent dosage.

Therapy.—The therapeutic indications are the same as for morphine and pethidine, but clinical trials suggest that dihydrocodeine (available as the bitartrate) is preferable when avoidance of respiratory depression is important and when morphine produces nausea and vomiting.

Toxic Effects.—Involuntary movements of limbs in anaesthetized patients. Release of histamine.

Antidote.—Nalorphine is effective.

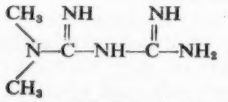
Contraindications.—The same as for morphine and pethidine. More information is needed on the histamine-releasing and constipating properties of the drug.

N.H.S. Basic Price.—12 1-ml. ampoules, 8s. 4d.; 100 30-mg. tablets, 14s. 2d.

Methformin

"Glucophage" (Rona Laboratories).

Chemistry.—This is N N dimethyl guanyl guanidine (or dimethyl diguanide), and has the following structural formula:



Pharmacology.—A recently introduced oral hypoglycaemic agent. Its mode of action and possible clinical uses are, to all intents and purposes, the same as those of phenethyldiguanide ("dibotin," phenformin)—see "To-day's Drugs" in *Brit. med. J.*, 1960, **1**, 641.

Therapy.—The daily dose of methformin required is larger than that of phenformin, and varies from 1 to 3 g. given in divided doses with meals. It is available in 0.5-g. tablets. The present indications for the use of either compound in the treatment of diabetics are very limited indeed, and they should be given only to patients under the care of hospital clinics.

Toxic Effects.—It is possible that the gastro-intestinal side-effects—such as anorexia, nausea, vomiting, or diarrhoea—which are so frequently caused by phenformin occur less often during treatment with methformin.

N.H.S. Basic Price.—0.5-g. tabs., 100 for 29s. 10d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Haemoptysis

SIR,—In the *Journal* of February 27 (p. 592) I read with surprise that Dr. R. N. Johnston and his colleagues conclude that it is unnecessary to follow-up patients who have had a haemoptysis provided they are carefully assessed at the first examination. This conclusion is based on their study of 324 patients presenting at a chest clinic with haemoptysis. This advice is so contrary to my experience and practice that it is necessary to study carefully on what evidence they base this conclusion. It appears that on only three occasions during the one- to two-year follow-up were they obliged to change their original diagnosis. This represents a very fine achievement in diagnostic skill in their original assessment, but had they not followed their patients up they would have missed two cases of active pulmonary tuberculosis and one of operable carcinoma of the bronchus. Surely this in itself justifies close observation and follow-up of such patients.—I am, etc.,

London, S.W.3. A. H. M. SIDDONS.

Maxillary Osteomyelitis in Infants

SIR,—I was very interested in Miss Florence Cavanagh's paper on osteomyelitis of the superior maxilla in infants (*Journal*, February 13, p. 468). In describing her 24 cases in the last twenty years, attention was drawn to the apparent rarity of reported cases of this condition in contrast to her own findings. The successful outcome of those treated by systemic antibiotics, combined with local treatment of the abscess cavity through polythene tubing, intranasally introduced, is most impressive, especially for the short duration of treatment required.

In the last six years I have had six cases of osteomyelitis of the superior maxilla under my care; these had been born in four different maternity units in the group. Four cases occurred within twelve months, in 1957–8, during a peak period of cross-infection in the then overcrowded neonatal nurseries, and all these infections were found to be due to *Staphylococcus aureus*. The cases presented the clinical features described, and the fulminating character of the onset was most noticeable, rarely more than 24 hours elapsed from the first symptoms until the full picture presented. All these cases were treated with prolonged systemic antibiotic therapy of some months' duration, based on the sensitivities reported at intervals by the laboratory. Locally the antibiotics were applied to the nares but not into the affected cavities. I have not felt happy about such prolonged use of antibiotics despite the satisfactory end-results, and very much welcome Miss Cavanagh's short and effective treatment.

None of the cases treated have so far shown any evidence of facial deformity, but in one instance it was necessary to make a small incision to remove a sequestrum. One baby showed some irregularity of eruption of the milk teeth on the affected side. The last five cases showed a culture of *Staphylococcus aureus*, phage-type 80, which was then prevalent in the nurseries. This specific infection was also found in three other cases of osteomyelitis, seven cases of pneumonia, and in numerous skin lesions in babies born in hospital at that time. All these infections developed within the first four months of birth. Intensive efforts to reduce cross-infection in the neonatal nurseries has apparently met with reward, as only one case of osteomyelitis, one of pneumonia, and a few minor skin infections have occurred in the same nurseries in the last 18 months.

As Miss Cavanagh stresses, correct diagnosis of this condition may well be overlooked. Equally to be stressed is that any serious infection, developing in the first few months of life in a baby born in hospital, may well be due to a hospital type of resistant organism. Should this prove to be so, then it is improbable that good response, at the present time, will be made either to penicillin or the tetracyclines, and valuable time may be lost in treating a seriously ill baby. I would be very interested to hear what percentage of Miss Cavanagh's cases were, in fact, born in hospital.—I am, etc.,

Royal Gwent Hospital, Newport, Mon. TERENCE A. BRAND.

Adenoidal Hyperplasia in a Mongol

SIR,—I recently had to anaesthetize a young mongoloid boy of 14 for multiple dental extractions. In view of the unusual findings on laryngoscopy, I thought a short account of the case might be of interest.

The boy showed the usual stigmata of mongolism but had a macroglossia which until after induction of anaesthesia had been difficult to assess because of lack of co-operation on the part of the patient.

On introducing the laryngoscope towards the base of the tongue, no epiglottis could be viewed. The whole of the oropharynx appeared to be filled with lymphoid tissue. Levering the tip of the blade forwards, a central line of cleavage appeared in this lymphoid mass, and lying immediately below an infantile epiglottis could just be viewed. With backward pressure applied to the trachea in the front of the neck, the glottis was with difficulty brought into view and an endotracheal tube introduced through the mouth.

When the oropharynx was examined in more detail the tonsils were seen to be grossly enlarged. At the lower pole of each tonsil there was a large projection passing forwards and medially. It was these two extensions meeting in the midline which had given such an unusual picture on the first introduction of the laryngoscope. A short nasopharynx is found in association with mongolism and this may be a factor in exaggerating the extent of the tonsillar enlargement.

The possibility of adenoidal hyperplasia of similar degree should be borne in mind in such cases when considering the choice of route for intubation. The apparent departure from the normal anatomical picture which first met the eye on laryngoscopy in this case is perhaps worthy of note. It is disconcerting if not a little alarming that at the moment of first view the patient is apnoeic from one's medication and wholly dependent on one's help for respiratory survival.—I am, etc.,

West Wales General Hospital, Carmarthen. G. PARRY WILLIAMS.

Cold Injury in the Newborn

SIR,—I have read with interest the paper by Dr. B. D. Bower *et al.* (*Journal*, January 30, p. 303), but I was disappointed that the confusion surrounding sclerema has been increased rather than dispelled. The authors recognize that the controversy has largely centred around terminology, yet it is odd that they quote Henoch,[1] who makes no mention of oedema though this featured in almost all their cases.

Underwood[2] referred to the condition as "skin-bound" and specifically stated that "feel of the skin and flesh is hard and resisting, but not oedematose."

Exposure to cold undoubtedly gives rise to oedema and hardening of the skin in neonates, but is generalized sclerema always due to cold? It would be of interest to know how many of Bower's cases had generalized sclerema without oedema, and whether any of these occurred in the later months of the year. Scleroedema would have been a better term for the oedematous babies. Naturally a rigid baby will have a low temperature, but this may be the effect rather than the cause. The distinction may not be entirely academic, because a case I reported in 1956[3] seemed to respond dramatically to cortisone and others have recorded the same experience. Bower and his co-authors make no mention of cortisone as a therapeutic measure and their case mortality for "sclerema" was 35%. Perhaps the administration of cortisone would have reduced it.—I am, etc.,

Stock, Essex. IAN G. WICKES.

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[1] Henoch, E., *Lectures on Children's Diseases*, translated by John Thomson, 1889, vol. 1. New Sydenham Society, London.
[2] Underwood, M., *A Treatise on the Diseases of Children, with General Directions for the Management of Infants from the Birth*, 1819, 7th ed. J. Callow, London.
[3] Wickes, I. G., *Arch. Dis. Childh.*, 1956, **31**, 419.

SIR,—The excellent survey by Dr. B. D. Bower and his colleagues (*Journal*, January 30, p. 303) has prompted me to recall a case of severe chilling in a baby, observed at the University Children's Clinic, Prague, in 1936.[1] The case is of interest because the infant sustained the lowest then recorded loss of body temperature and survived. It also shows that the danger of accidental chilling of babies is not confined to the immediate postnatal period.

A one-month-old, breast-fed baby was referred by his doctor as "moribund" on a cold night of October. In the afternoon the infant, who had been thriving well, had suffered a superficial cut on his forehead. He cried, became breathless, and the mother exposed the sparsely clad baby to the cold air by the open window in order to revive him. Then he was tightly wrapped in a feather cushion, but the condition deteriorated. On admission the baby was in a state resembling death, icy cold to touch, with patchy induration of the skin. Pulse and respiration rate were slow and irregular. The rectal temperature taken with the "Rana" thermometer used at the clinic, ranging from 18° C. to 43° C. (64°–109° F.), was found to be 64° F. (18° C.). The wide range of the thermometer scale proved not as unnecessary as previously thought.

After administration of cardiac stimulants the baby was put into a hot bath at 86° F. (30° C.) and the water temperature was gradually raised to 100° F. (38° C.) and eventually to 108° F. (42° C.). The body temperature rose after half an hour to 73° F. (23° C.) and reached eventually in three hours 99° F. (37° C.), but remained unstable without warming. The skin reddened, the induration disappeared, pulse and respiration rate quickened. However, the baby remained in deep sopor with hypotony and loss of reflexes. On the third day he had a convulsion with right-sided nystagmus and facial palsy. Lumbar puncture revealed normal fluid under slightly increased pressure. This cerebral state persisted for five days, but loss of reflexes, nystagmus, and drowsiness for several weeks. Three months after the incident the baby had completely recovered.

The lowest body temperature in human beings compatible with survival was recorded to be 68° F. (20° C.), and in the experimental animal in various species between 64° F. and 82° F. (18°–28° C.). The described case seems to indicate that recovery in the young infant is possible from a still-lower degree of chilling than in the adult. However, death may occur at a much lesser degree of chilling because the thermo-regulatory centres seem to act only within certain individually determined limits. The individual resistance to extreme chilling together with other factors like sleep, hunger, and fatigue may be of greater influence on the loss of body temperature than the temperature of the environment. In this connexion it is of interest to recall the rather bold experiments of Raudnitz[2] who has shown that healthy infants left uncovered for half an hour did not lose more than two degrees centigrade of their temperature. Even when icy cold water was poured over babies their body temperature was only slightly lowered. The extreme loss of temperature seems the result of multiple factors.

I agree with Mann[3] and Dr. B. D. Bower and his colleagues that gradual rewarming is the method of choice, especially in cases of longer lasting chilling. However, experiments in dogs have shown that after reducing the body temperature to 18° C. (64° F.) death can be best avoided by quick rewarming of the animal in a hot bath. Therefore, as in our case, this treatment may be advisable, if resuscitation is begun shortly after extreme chilling.

Though being familiar with the symptomatology of cold injury I have seen in our large hospital material during a period of sixteen years only one single case of this condition. I wonder what particular circumstances cause the high incidence of chilled babies in the Brighton and Birmingham area.—I am, etc.,

West Middlesex Hospital, Isleworth, Middlesex. M. DYNSKI-KLEIN.

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[1] Klein, M., *Med. Klin.*, 1936, **32**, 1426.
[2] Raudnitz, R., *Z. Biol.*, 1888, **24**, 423.
[3] Mann, T. P., *Lancet*, 1955, **1**, 613.

Corticosteroid Therapy in Ulcerative Colitis

SIR,—I have read Dr. S. C. Truelove's excellent article (*Journal*, February 13, p. 464) with great interest. Having been very disappointed with the effect of cortisone in ulcerative colitis, I began a trial of oral prednisolone at this hospital in January, 1957. The aim was to determine whether remission could be induced, whether a maintenance dose would reduce the tendency to relapse, and whether a threatened relapse would be aborted by temporary increase in dosage. To date the results have been most encouraging,[1] and we now have records of some forty consecutive patients successfully treated along these lines. It remains to be seen whether in time failures will be encountered, but so far we have not had one.

Our experience indicates that a large initial dose (40 mg. daily for one to two weeks) spares the patient the inconvenience of a nightly rectal drip, that maintenance therapy (usually between 5 and 15 mg. daily) is beneficial, and that threatened relapses can be cut short by increasing the dose to 40 mg. daily for a few days.—I am, etc.,

West London Hospital, London, W.6. A. MORTON GILL.

REFERENCE

[1] Morton Gill, A., and Kenyon, W. I., *Amer. J. Gastroent.*, 1959, **32**, 701.

Steroids and Steatorrhoea

SIR,—In his highly speculative article entitled "Anterior Pituitary Deficiency in Disorders Associated with Steatorrhoea" (*Journal*, February 20, p. 529) Dr. J. N. Mickerson draws sweeping conclusions from singularly little fact. In the clinical description he states

that five of the seven patients showed increased pigmentation of the skin, but goes on to say that all had features of pituitary insufficiency—an association which is extremely rare, since it implies the preservation of pituitary melanocyte-stimulating hormone.

The biochemical evidence that is produced is on no stronger ground, as is indicated in the annotation (p. 559) on this subject. Plasma 17-hydroxycorticoids and urinary 17-ketogenic steroids, which provide the only really satisfactory basis for the assessment of adrenal cortical function, do not appear to have been carried out. Lepore[1] (quoted in Dr. Mickerson's paper) reported that in all his cases of steatorrhoea in which plasma 17-hydroxycorticoids had been estimated there were normal resting values and a normal response to corticotrophin. Eik-Nes *et al.*[2] reported a similar finding, and a case investigated by myself also showed a normal plasma corticosteroid response. In short, there is no real basis upon which to invoke a state of secondary adrenal insufficiency. Moreover, the concept of "anterior pituitary exhaustion" only serves to cloud the issue and on present evidence must remain a myth.—I am, etc.,

St. George's Hospital Medical School, London, S.W.1. JOHN S. JENKINS.

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2 Eik-Nes, K., Sandberg, A. A., Migeon, C. J., Tyler, F. H., and Samuels, L. T., *J. clin. Endocr.*, 1955, **15**, 13.

Carob-seed Flour

SIR,—Your annotation on diaphragmatic hernia in infancy (*Journal*, February 20, p. 560) prompts me to point out that feeds are better thickened with carob-seed flour ("nestargel") than with cereals. The former is not digested in the stomach and so maintains its thickening function for a much longer period. Experience with nestargel suggests that the time during which the infant must be kept continuously sitting up (much the most trying part of the treatment) is greatly shortened or sometimes unnecessary, but for reasons I do not comprehend the flour cannot be prescribed on an E.C.10. It is supplied free to hospitals and there is no difficulty with in-patients, but on discharge parents in this area may have to make journeys totalling over 40 miles (64 km.) for no other purpose than renewing their supplies.

Surely the time has come when this extremely useful medicament is made freely available to those who require it.—I am, etc.,

Tunbridge Wells. N. M. JACOBY.

"A Case of Juvenile Cirrhosis"

SIR,—I have read with interest the clinicopathological conference on "A Case of Juvenile Cirrhosis" (*Journal*, February 27, p. 631). However, I believe my work has been misinterpreted. I did not attempt to induce cirrhosis or lenticular degeneration by means of copper. I gave a diet of maize and copper acetate, with and without *p*-dimethylaminoazobenzene (butter-yellow) to rats, and found that copper acetate had an inhibitory effect on hepatic tumour development.[1] In fact I stated that animals given copper without butter-yellow had a normal liver and that copper *per se* is not a cause of cirrhosis. In any event the theory put forward by Mallory, Parker, and Nye[2] that copper is capable of inducing cirrhosis has been refuted by several workers besides myself.

The paper[3] referred to by Dr. A. G. E. Pearse was concerned with the histochemical demonstration of copper. The figures accompanying it were to illustrate the appearance of copper in the tissues demonstrated by these methods, and the two figures from the group of animals given copper alone did not show any abnormality apart from copper deposition. Finally, I would also like to point out that the histochemical tests for copper can be performed satisfactorily on tissue that has been fixed and embedded in the routine way.—I am, etc.,

Department of Pathology, The Medical School, Birmingham, 15. J. S. HOWELL.

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2 Mallory, F. B., Parker, F., and Nye, R. N., *J. med. Res.*, 1920–1, **42**, 461.
3 Howell, J. S., *J. Path. Bact.*, 1959, **77**, 473.

Diffuse Interstitial Pulmonary Fibrosis

SIR,—In his article (*Journal*, February 13, p. 443) on chronic diffuse interstitial fibrosis of the lungs, Dr. J. G. Scadding draws attention to two interesting points: first, the differentiation of this syndrome from the more acute one of Hamman and Rich, and, second, the possible association of chronic diffuse interstitial fibrosis of the lungs with liver disease.

In 1952 a woman aged 54 was admitted to hospital with haematemesis. She gave a history of four previous haematemeses. She had her spleen removed in 1946, and the operation notes remark on the enlarged liver. The histology of the spleen is described as being consistent with portal hypertension. She responded to blood transfusion, and barium swallow showed appearances of oesophageal varices.

In 1953 she was readmitted with a further haematemesis. At that time she gave a history of dyspnoea on exertion, and crackling, rustling crepitations at the lung bases were noted for the first time. In 1956 a further small "bleed" led to her admission, and by now she had finger-clubbing, much more widespread persistent crackling crepitations, and progressive dyspnoea. She was regarded as having chronic cirrhosis of the liver and chronic interstitial pulmonary fibrosis. From this time on to her final admission to hospital in 1959 she developed marked "drum-stick" clubbing, progressive dyspnoea, and increasingly widespread crackling crepitations until these were audible in all parts of the chest. She deteriorated and died in March, 1959. Permission for necropsy was refused.

Of two other cases of clinically typical chronic interstitial pulmonary fibrosis, one has been unassociated with any other pathology, and the other has occurred in a woman suffering from hypopituitarism.—I am, etc.,

The General Hospital, Dewsbury, Yorks. GODFREY B. TAIT.

Photographing a Birth

SIR,—I have read in the *Scottish Daily Mail* that an expectant mother who is going into St. Mary Abbots Hospital, London, will be photographing the actual birth of her child because both she and her husband "are very thrilled about the baby. We feel it is a moment in our lives that is so vital that we should have a permanent record of it from beginning to end."

I am amazed and disgusted at the hospital allowing lay people, and patients at that, to take such pictures. It is an outrage and a complete invasion into the privacy of the hospital. From the medical point of view what is there to be gained? From the couple's point of view I hope they will reconsider their intentions; and from the hospital's point of view I hope it will reflect carefully on its decision to allow the intimacy and

privacy of a confinement from being turned into a "circus." I also hope that the doctors on the case will see that such a "performance" is nothing short of a disgusting piece of bad taste and will either prohibit the pictures being taken, thereby treating it with the contempt it deserves, or, failing this, refuse to attend the case.

Hospitals are there for the purpose of looking after the health and welfare of patients and certainly not to pander to the whims of individuals.—I am, etc.,

Glasgow, S.W.3. ARNOLD B. COWAN.

Proteins of the Liquor Amnii

SIR,—I read with great interest the article by Drs. T. M. Abbas and J. E. Tovey (*Journal*, February 13, p. 476) on the proteins of the liquor amnii. During the past year, whilst assisting Dr. A. H. C. Walker with work on the prediction of severity of haemolytic disease of the newborn by spectrophotometric study of liquor amnii,[1 2] I have taken the opportunity of examining liquor with respect to bilirubin, protein concentration, electrophoresis (paper and cellulose acetate), and for the presence of antibodies (anti-D) in over 50 cases. Although a more detailed account of this work will be published elsewhere, from the results obtained so far, and since there is some further literature on this subject not mentioned by Abbas and Tovey, I would like to make some comments on the suggestions they made as a result of their investigations.

With regard to the protein pattern of liquor amnii obtained by paper electrophoresis, Mentasti[3] has shown that different results are obtained when free micro-electrophoresis is used. Hanon *et al.*,[4] Candiani,[5] Tapparelli and Franco,[6] and Barbanti,[7] all obtained different results using paper electrophoresis. Mentasti also states that there is a progressive increase in the gamma globulin fraction after the sixth month of pregnancy, and at this time all five serum protein fractions can be made out. So far, except in three cases of hydrops foetalis when all five protein fractions were found, I have only been able to detect four of the five proteins, alpha-2 being consistently absent, in liquor obtained at 32 weeks. What is more, Mentasti gives results which show significant correlation between liquor and foetal proteins, but not between liquor and maternal serum proteins, as the dialysis experiment performed by Abbas and Tovey would suggest. It would be very interesting to know what result is obtained when foetal serum is dialysed across the foetal membranes as well.

In cases of rhesus incompatibility, I have evidence to suggest that the protein concentration of the liquor increases (compare Mentasti's two cases), and that the umbilical cord is a possible source of protein reaching the liquor. Compared with the one case of hydrops foetalis given by Abbas and Tovey, in which the concentration of liquor protein was 300 mg./100 ml., I have found values of over 1,000 mg. in three cases, and in another it rose from 225 mg. at 32 weeks to 630 mg. at 36 weeks. The length of time the foetus has been dead and the time at which the liquor is obtained probably accounts for the difference in these figures.

Finally, with regard to the suggestion by Abbas and Tovey that the liquor amnii is a possible source of antibodies and foetal nutrition, I should like to bring attention to the work of Bangham *et al.*[6] on the selective placental transfer of serum proteins in the rhesus monkey. This has a placentation similar to that of man towards term, and, by using labelled homologous serum proteins, they present evidence that liquor amnii plays an unimportant role in the transfer of whole serum proteins. Labelled maternal serum proteins injected into the liquor could not be detected in the foetus 24 hours later. Before trying to find out how antibodies could reach the liquor and where they go to, it seems obvious that one should first try to find out if they are there. On over 30 occasions now I have detected anti-D antibodies in the liquor, but not on all occasions when the mother had detectable antibodies. Where the maternal serum titre was 128 or over they were nearly always detected, the highest titre recorded in the liquor so far being 128 in a case of hydrops foetalis. Free antibodies have also been detected in the cord serum on these occasions, however, and if the work of Bangham can be applied to man one can only conclude that they reach the liquor *via* the cord.—I am, etc.,

Department of Pathology, St. Mary's Hospitals for Women and Children, Manchester, 13. A. E. WILD.

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5. Hanon, F., Coquoin-Carnot, M., and Pignard, P., *Le Liquide Amniotique*, 1955. Masson, Paris.
6. Tapparelli, E., and Franco, G., *Riv. Ostet. Ginec. prat.*, 1956, **38**, 264.
7. Barbanti, A., *Minerva ginec. (Torino)*, 1956, **8**, 708.
8. Bangham, D. R., Hobbs, K. R., and Terry, R. J., *Lancet*, 1958, **2**, 351.

Cardiac Arrest and the Brain

SIR,—You quote in your leading article on cardiac arrest (*Journal*, February 20, p. 558) a case in which ventricular fibrillation was present for 90 minutes, and was followed by complete recovery, in spite of cardiac massage not being instituted during this period.[1] However, ventricular tachycardia was also present, and the duration of the fibrillation was unknown. The authors point out that the presence of ventricular complexes in the E.C.G. does not necessarily indicate effective contraction, but this seems to have been so in this case. That the (? carotid) pulse was impalpable is perhaps not surprising in view of the profound hypotension and a heart rate of 200. They do not state whether the incision bled at the commencement of the thoracotomy.—I am, etc.,

Brompton Hospital, London, S.W.3. ALAN GILSTON.

REFERENCE

1. Schlachman, M., Sorbello, N., and Haddad, S., *Arch. intern. Med.*, 1958, **101**, 650.

Myelosclerosis

SIR,—Your leading article on myelosclerosis (*Journal*, February 27, p. 625) is misleading in several ways, but I wish to draw attention only to the remarks made on treatment. The statement is made "... and destructive drugs like those used for the control of chronic myeloid leukaemia should also be avoided. The importance of accurate diagnosis is thus evident, since treatment suitable for chronic myeloid leukaemia will make the myelosclerosis patient worse." This statement is quite contrary to the facts. It is correctly stated earlier in the article that the blood count shows an increased white-cell count with early granulocytes and normoblasts present. If the increase in the white count is considerable—for example, 20–40,000 per c.mm.—*x*-ray treatment to the enlarged spleen, or "myleran" (busulphan) by mouth, produces a remarkable improvement in the patient's health, the abnormal tiredness disappearing, the cramps in the feet and legs diminishing, and the spleen decreasing in size, sometimes very

considerably, with a consequent relief of the symptoms due to the enlarged spleen. This improvement occurs regardless of the degree of osteosclerosis or myelosclerosis. The good effect of treatment lasts a varying period of time, as in typical cases of chronic myeloid leukaemia, and several courses of treatment may be given. The effects of the treatment are sometimes more dramatic and longer lasting than in chronic myeloid leukaemia. Since busulphan became available, this drug is probably superior in its effect to *x*-ray treatment of the spleen.

Those patients with osteosclerosis or myelosclerosis who have a normal or diminished white-cell count are very difficult to treat, and no doubt *x*-ray treatment and busulphan may be contraindicated, because of the possibility of producing severe neutropenia or thrombocytopenia. But these cases are not more than about one-third of all cases of myelosclerosis.

The reason for this letter is that, if the advice in your leading article is followed, about two-thirds of the cases of myelosclerosis will not receive what is at present by far the most effective treatment.—I am, etc.,

Charing Cross Hospital,
London, W.C.2. R. A. HICKLING.

Shoes and Feet

SIR,—Surveys of children's feet continue to be made with monotonous regularity, and the results constantly show the association of ill-fitting shoes and foot defects. That one is the cause of the other cannot be proved by such evidence. What needs to be repeated is the experiment known as the Ealing Shoe Scheme, of which there was no mention in your leading article (*Journal*, February 13, p. 488). This important work showed what happened to 164 children's feet when kept in well-fitting shoes over a period of two years. Corns, callosities, and cramped toes practically disappeared, and the angulation of proximal hallux valgus lessened considerably.

Your leading article stated that there are people whose footwear cannot be criticized, but in my experience there are very few children whose shoe-wearing habits are above criticism. Children's shoes are so designed that when correctly fitted at the time of purchase they will allow unrestricted growth for 4–6 months; however, inquiry will show that the universal habit of keeping new clothes for best wear applies to children's shoes too. Any one pair of shoes can be worn for as long as one year or more—namely, four months' best wear, four months' school wear, and four months to play in at home after school and at the week-ends. Very few parents allow their children to wear new shoes straight away every day, as they should, discarding them after four months for another new pair.—I am, etc.,

Area Health Office,
Town Hall,
Ealing, London, W.5. CATHARINE HOLLMAN.

REFERENCE

[1]Craigmile, D. A., *Brit. med. J.*, 1953, **2**, 749.

SIR,—As a chiropodist who has been over thirty years in practice and has spent a lifetime lecturing on feet, I cannot allow your leading article entitled "Shoes and Feet" (*Journal*, February 13, p. 488) to pass without comment. I would like to make five points:

(1) By far the greatest amount of pain and disability are caused, not by *deformities* of the feet, but from the pressure lesions (corns, callus, etc.) which arise from them. Even plantar lesions are to a large extent the result of toes buckled by inadequate footwear.

(2) A high proportion of patients seeking treatment from chiropodists can only be given any considerable or lasting relief if they are willing to improve their footwear, and a very large number need no other form of treatment than a change of shoes.

(3) Far too much time and effort have been expended on the red herring of trying to decide what is normal and what is deformity. Surely there is no such thing as a normally shaped foot, any more than there is a normal face. Should not the criterion be—"does it serve its owner efficiently and painlessly?"

(4) Foot health is very largely dependent on adequate function of the toes, especially of the great toe. It follows from this that two things are of paramount importance if trouble is to be avoided: First, the development of this function should not be inhibited—and civilized life from birth onwards can hardly be said to encourage it—though in fact a high proportion of the population never do develop it. Second, once it has been acquired, footwear should not prevent its being maintained and used.

(5) Shoes can only give freedom for toe function if they are held on the foot in the proper manner—that is, by band, bar, strap, or lace over the dorsum of the foot—and *not* by a grip between the heel and the toes, as in "courts," open "casuals," and their large family of hybrids.

—I am, etc.,

London Foot Hospital,
London, W.1. M. D. ENGLAND.

SIR,—We were interested to read the leading article "Shoes and Feet" (*Journal*, February 13, p. 488).

In a foot survey which was carried out a few years ago by our fitting research department in conjunction with the medical and education authorities of the Somerset county council, some of the findings proved the lack of appreciation on the part of the average parent of the importance of correct shoe-fitting for their children.

When children taking part in this survey were asked if they were present when their shoes were bought, nearly 30% said that they were not. Out of 1,250 boys and girls whose feet were examined by Mr. Hedley Hall, F.R.C.S., Mr. T. Price, M.B., M.Ch., and our own team of foot-fitting experts only 30% were wearing shoes of the correct size and fitting.

We are convinced that the only way to ensure that children have correctly fitting shoes is for them regularly to be taken by their parents to a reputable shoe-retailer who stocks well-made and correctly designed children's shoes in half-sizes and a choice of width fittings, and where the staff have been trained to measure feet correctly on a properly designed foot-fitting device.

Perhaps one of the "faults" with children's shoes these days is that, owing to improved shoemaking techniques and the development of soling materials which are of a very hard-wearing nature, they do not wear out. This means that parents are inclined to forget how long the children have been wearing them and do not realize that they have been outgrown. Regular measuring and checking is the only answer to this problem.

We are delighted to see that in most counties throughout the country those responsible for health and education are concentrating on foot-health education directed at parents, for it is the parents who most need to be educated in this most important subject. Some of the leading branded shoe manufacturers in this country now produce excellent children's shoes all in

half-sizes and—equally important—in up to five widths. These are stocked by retailers trained and competent to fit them properly, provided they receive the essential co-operation of the parents.—I am, etc.,

C. & J. Clark Ltd., Street, Somerset. J. ANTHONY CLARK, Sales Director.

Pulseless Disease

SIR,—I have just now read, with pleasure and profit, the article on pulseless disease by Mr. J. M. Pahwa and his colleagues (*Journal*, December 26, p. 1439). Please permit me to point out an inaccuracy. The authors claim that this is the first reported case of pulseless disease from India. As a matter of fact, the first case report was by Shikhare.[1] The next was by Sen Gupta and Ghosh,[2] and the third report, consisting of three cases, is by Misra *et al.*[3]—I am, etc.,

Department of Clinical Medicine, King George's Medical College, Lucknow, India. S. S. MISRA.

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2 Sen Gupta, S. N., and Ghosh, J. C., *Brit. med. J.*, 1957, **1**, 137.
3 Misra, S. S., Prakash, S., and Agrawal, P. L., *Amer. Heart J.*, 1959, **57**, 177.

SIR,—May I bring to your attention that Dr. R. S. Rajagopalan and myself reported about a case of aortic arch syndrome in the *Journal of the Indian Medical Association*?[1] That case is another one that can be added to the list of cases of aortic arch syndrome already reported from India.—I am, etc.,

East Fortune Hospital, North Berwick. M. S. N. RAO.

REFERENCE

1 Rajagopalan, R. S., and Rao, M. S. N., *J. Ind. med. Ass.*, 1957, **28**, 523.

Safety Harness for Car Occupants

SIR,—Following my letter (*Journal*, November 14, p. 1020) I have received a considerable number of inquiries, at first from this country and later, when the *Journal* got around the world, from as far afield as the gentle isle of Tasmania. I have sent my correspondents the names of the makers of reliable British safety harness. I have not been able to give them the names of British car manufacturers or the agents who are prepared to supply and fit reliable harness suitable to their particular design of car. In an endeavour to get this information my impression is that even the suggestion to manufacturers and agents that a reliable harness adds to the safety of the occupants of their cars is in the worst possible taste, and certainly a very bad selling-point for their own product. Yet the industry and the car-buying public must now know that injuries to car occupants can be prevented or their severity lessened, if after a crash the car seat is still firmly anchored to the floor and its occupant maintained in the seat and not violently ejected from it. The avoidance of this hazard is of particular importance to the safety of occupants in small British cars.

The position as I now understand it is that the makers of reliable British safety harness cannot afford an expensive and continuous national advertising campaign, nor can they provide a national cover for the prompt fitting of their equipment. Hence obtaining the right equipment and getting it securely and comfortably fitted to match the body and seat design of a particular car now results in so much trouble and expense that relatively few owners will go through these difficulties. Although it would be unreasonable to expect the British motor industry to undertake a national advertising campaign for safety harness, it *could be* to the advantage of their sales, both at home and abroad, to advertise (perhaps in the smallest print, in the corner of their normal advertisements) their willingness to supply and fit reliable safety harness suitable to their particular design of car. This would cost them nothing, it undoubtedly would save hospital surgeons and nurses a lot of painstaking work and keep more car owners alive and so able to buy more cars.

Perhaps the Society of Motor Manufacturers and Traders could, through this *Journal*, explain to my many correspondents the views of the British motor industry on this matter. Judging from the letters, my correspondents cannot understand what they interpret as a "passive resistance" of the industry to this safety equipment.—I am, etc.,

Birmingham Accident Hospital, Birmingham, 15. WILLIAM GISSANE.

Survival in a Nuclear War

SIR,—Except to those whose powers of reasoning are bemused by power politics, partly home-made, partly adopted from N.A.T.O. allies, it is obvious and particularly so to members of our profession that if this country should become involved in a nuclear war there is no defence which will save the majority of its population from extinction.

What we wait for is a declaration by our Government that under no circumstances will it authorize the use of nuclear weapons against human beings. Instead of this it wavers in hopes that its rivals in world influence will refrain from a nuclear attack on Britain from fear of retaliation, while it piles up its own offensive nuclear weapons with help from the United States. In this policy it is taking part in the greatest political folly in the history of European civilization and is wasting a large proportion of its wealth on defensive plans that are illusory.—I am, etc.,

Faringdon, Berks. K. W. MONSARRAT.

Radioactivity in our Environment

SIR,—The inevitability of progress in science towards the material welfare of humanity was a *fin de siècle* axiom. No greater fallacy has ever been imposed on a credulous world. Science is becoming a menace in many respects, not the least medically. Since the catastrophic use of atomic fission in 1945, the amount of radioactivity in the atmosphere has steadily increased throughout the world.

There is no basic level below which radiation is safe and above which it becomes dangerous. It is possible that this level is already passed, but, whether this is so or not, it is inevitable that it will be passed. We have now nuclear submarines and even ships, presumably discharging their dangerous products to poison the sea; nuclear reactors on land contaminating, slowly but surely, the atmosphere and everything contiguous, and atomic energy being canvassed in every country as the "thing of the future"—all this must inexorably raise the titre of radioactivity in the air we breathe and in which we are immersed. This is without the folly of nuclear explosions, which, to her credit, Russia has been attempting to outlaw. One feels that as doctors we ought to add such authority and prestige as we have to discourage France from what many thinking people consider

to be the superlative folly of having her own nuclear bangs, for this may trigger off a further series of Russian, American, and English explosions for which science is responsible but which scientists cannot control, either in their immediate or more remote effects.

Result, increased leukaemia, which is as inevitable as to-morrow, and mutations rising like weeds. These sad thoughts are prompted by a baby I delivered recently, with a craniocele, an imperforate anus, and unmistakable stigmata of deficiency. I sent it to hospital and was horrified to learn that there were, in the hospital, 16 further infants with developmental abnormalities. I have heard recently of a number of cases of leukaemia, and I think it would be a wise and timely precaution to make leukaemia a notifiable disease, in order that we may assemble some definite statistics about the disease.

I have a patient with carcinoma of the thyroid gland from *x*-irradiation 25 years ago for thyrotoxicosis, when that now-abandoned therapy was fashionable. What assurance have we got that within a decade medical science will not look back with horror on the introduction into the human body of radioactive isotopes? The schism between the biologist who looks upon the increasing radioactivity with disfavour and the physicist who under the aegis of Big Business and Governments is rapidly disseminating the indestructible and indisposable products of nuclear fission or fusion is complete. When I tackled a nuclear physicist on these points recently, he admitted ruefully that when the life of a reactor is finished the radioactive residue is there, is highly active, and must poison everything about it, and, wherever it is disposed of, it will continue to poison for a half century.

There should, of course, be a supranational World Health Authority, with real authority to limit any country in the amount of radioactivity it produces, with a panel of eminent scientists in control, for it is certain that science is very uneasy in the forces it has released in the last 20 years, and to permit the politician to retain control of these cosmic forces may be calamitous. It seems to me that the future will see the harnessing of solar energy, and that the evocation of nuclear energy will be, we hope, a transient and unfortunate adventure in science.—I am, etc.,

Rothwell Haigh,
Near Leeds,

C. E. GOLDSBOROUGH.

The Gas Man Cometh

SIR,—It is evident that the examination for the diploma in anaesthetics serves no useful purpose; it is also evident that its retention by the Faculty of Anaesthetists serves only to augment the financial resources of the Royal College of Surgeons.

Medical practitioners who intend to make a full-time career of anaesthetics will naturally be expected to obtain the higher qualification, while those who merely want to give the odd "dope" will find that a specialist qualification—even a low one—is unnecessary, nay, superfluous. The possession of a diploma, unlike that of other specialties, confers nothing on the recipient, other than the doubtful privilege of adding two more letters to his name. Printers confuse it with an arts degree; the public, especially the more patriotic, consider it some sort of Army title or territorial distinction; while the Americans, generous to a fault, hail it as district attorney. Hospital authorities, more and more, insist on the possession of a fellowship, when individuals apply for the post of senior registrar or registrar.

In the past twenty years, anaesthesia has come a long way, and, within that period, individual anaesthetists, rather than the Faculty as a body, have made magnificent advances in skill and research. As a result of this, one would expect that their position would be on a par with the surgeon. Instead we find the same old set-up that must surely have prevailed on that October morning in 1846 in Boston. The anaesthetist, in spite of his diploma or even fellowship, is still "the man at the top of the table," the "gas" man, the butt for the surgical humour, and the target for surgical temper; assisted by the most junior probationer in the theatre, handling the most important subject in the drama—the patient. And the answer to Chesterton's query:

"And what is theirs . . .
How little is the prize they win, how mean a coin for these"

—a few guineas, picked up like crumbs from the rich man's table.—I am, etc.,

Wellington,
New Zealand.

T. J. CROWLEY.

Congenital Dislocation of the Hip

SIR,—As a family doctor, I can confirm Mr. Denis Browne's letter (*Journal*, February 20, p. 564) stating that it is possible to diagnose congenital dislocation of the hip in the neonatal period. By looking for this condition at my first examination of babies, I have found four cases in the past five years.

I have not diagnosed C.D.H. in the way described by Mr. Denis Browne. Instead, I flex the hips to 90° and then abduct them. When C.D.H. is present, the head of the femur is felt to enter the acetabulum and this is commonly accompanied by a loud click (Ortolani's sign), which may be heard across the room. Radiographic examination is not necessary to confirm this diagnosis. Mr. A. C. Bingold has treated these babies with Frejka splints, which are applied by the mother over the nappy for four to six months, after which the hips are normal. This procedure is so simple that even a gipsy mother has coped happily with her baby at home. Mr. Bingold has kindly drawn my attention to *Congenital Dysplasia of the Hip Joint and Sequelae*, by Vernon L. Hart,[1] which describes this approach in detail.—I am, etc.,

St. Paul's Cray,
Kent.

JOHN WOODALL.

REFERENCE

[1] Hart, V. L., *Congenital Dysplasia of the Hip Joint and Sequelae*, 1952. Charles C. Thomas, Springfield, Illinois.

New Drugs for Depression

SIR,—My attention has been called to some correspondence regarding the use of drugs for depression. I am referring particularly to a letter (*Journal*, January 16, p. 200) in which Drs. F. A. Bleaden and G. Czekanska report two instances of respiratory difficulty following electroconvulsive therapy when their patients were concurrently receiving phenelzine. I would like to call attention to certain factors which may have contributed to the problems encountered.

In their Case 1 they seem to make the careful distinction that unmodified electroconvulsive therapy was given and toleration of the treatment was normal prior to administration of phenelzine. From the description, it is therefore reasonable to believe that the electroconvulsive therapy given on November 28 while phenelzine was being administered was modified with thiopentone and suxamethonium. In Case 2 a very similar incident occurred,

and in the description of the treatment the doctors very carefully describe modification of the treatment with thiopentone and suxamethonium specifically. The reactions described are practically characteristic of the not-infrequent occurrence of respiratory sluggishness associated with muscle-relaxing suxamethonium and its derivatives as well as the older curare preparations. The prompt response of the patients to administration of oxygen and niketharnide is also characteristic of the late reactions to the muscle relaxants. It is therefore questionable whether phenelzine could have had any direct effect under such circumstances.

In our rather extensive experience with antidepressant drugs and electroconvulsive therapy we have encountered no difficulty in combining electroconvulsive therapy with concurrent administration of any of the antidepressants—the hydrazides (monoamine oxidase inhibitors) or imipramine. We have encountered no difficulty with such treatment in well over 100 patients. It must be pointed out that we have steadfastly avoided the use of any muscle relaxants because of the tendency to production of respiratory embarrassment, and have employed manipulation of the electric-current level for prevention of skeletal injuries.

I would point out also that the dose of 45 mg. three times daily is about three times the maximum recommended dose of phenelzine. In Case 2, in which this large dose of phenelzine was given and the electroconvulsive therapy administered six days after discontinuing the phenelzine—in the absence of any hypotensive effect or other toxic reaction which might remotely be interpreted as the result of administration of phenelzine—it hardly seems relevant to attribute the respiratory embarrassment to phenelzine when sufficient cause is present in the use of suxamethonium.

It must always be remembered that, while electroconvulsive therapy under the best circumstances is one of the safest recently acquired blessings of humanity, in sensitive individuals it can of itself produce respiratory and cardiac effects that are frightening, though fortunately very rarely fatal. It is necessary, therefore, to exercise extreme discrimination in attributing any untoward reaction that may occur with such treatments to any special medication or condition of treatment.—I am, etc.,

Longview State Hospital, Cincinnati, 16, Ohio. DOUGLAS GOLDMAN.

Phenoxymethylpenicillin and Drowsiness

SIR,—Dr. W. M. C. Hallinan (*Journal*, November 28, p. 1183) mentions the soporific effect of phenoxymethylpenicillin. A few weeks ago I prescribed 240 mg. of penicillin V a day to a 30-year-old lady pianist suffering from sore throat. She was afebrile. Three days later she returned rather alarmed, complaining that after the first day's dose she had slept 20 hours at one stretch. Her throat felt much better on waking up. However, for the next 24 hours she was unable to concentrate on her piano-playing. In this case the soporific effect of penicillin V was desirable, as it would be in a lot of cases that deserve to receive penicillin. I hope that more interest will be directed on this subject in your columns.—I am, etc.,

Department of Internal Medicine, Augusta Victoria Hospital, Jerusalem. VICKEN KALBIAN.

Mrs. Harvey's Portrait

SIR,—There used to be at Burley-on-the-Hill a portrait in oils of Mrs. Harvey, wife of the discoverer of the circulation of the blood, but it was destroyed by fire towards the beginning of this century. I should very much like to get a description from someone who saw it before its destruction, even more to find a photograph or painted replica of it. I should therefore be most grateful to anyone who can and will send me information.—I am, etc.,

Broomfield, Yarnton, Oxon. KENNETH J. FRANKLIN.

POINTS FROM LETTERS

Tendinitis

Dr. C. LANDON SMITH (Bedford General Hospital) writes: The use of the expression tenosynovitis to describe the non-suppurative condition of pain and crepitus occurring over the radial border of the lower forearm is both inaccurate and misleading. This condition, which appears to affect the long extensors of the wrist in the situation where they pass under the bellies of the short extensor of the thumb and of the long abductor muscle, is a tendinitis, as there is no synovial sheath surrounding these tendons at this level. Thumb movements are usually painless, but wrist movements are reduced and painful. The treatment of the tendinitis is, I believe, scattered injections of hydrocortisone into the region of the tendons followed by restricted use. Immobilization in plaster, although temporarily relieving the pain, does not appear to relieve the condition, the pain returning following removal of the plaster.

Auscultation on the Gramophone

Dr. M. J. MORRISSEY (Parramatta, New South Wales) writes: I have recently seen some correspondence in the *B.M.J.* concerning the desirability of having the various respiratory and cardiovascular sounds recorded on gramophone records. To my own knowledge this was done here in Sydney some 15 years ago by Dr. E. H. Stokes, who produced a set of 28 double-sided records of the various cardiovascular and respiratory sounds, together with a spoken commentary and a printed booklet describing them. This was before the advent of the L.P. record, but in all there were some 150 different sounds recorded, and the set was available in album form to students and others interested.

Shoes and Feet

Dr. L. A. NICHOLS (Sidcup) writes: Your leading article (*Journal*, February 13, p. 488) discusses shoes and feet as if an amputation had been carried out through the Achilles tendon. The possible causes of deformities and other troubles of the feet are considered as attributable to unsuitable footwear "or partly determined by inherent weaknesses of the foot itself combined with the restricted stereotyping of foot movements which civilized life imposes." But not only the muscles of the foot, the musculature of the whole body is involved in walking; and responsibility must also be accredited to the brain, the organs of sight, and hearing. Apart from cases due to gross external forcible limitation of growth and movement mechanical defect must arise due to alteration of the tension of the musculature. . . . The presence or absence of pain depends on this increase of muscle tension. . . . Thought and muscular reaction are related. The conversion of psychic into motor excitement, or motor impulses to psychic energies, is acknowledged.

Mr. E. R. MOORE (managing director, Messrs. Moore Bros. Ltd., Salisbury) writes: With reference to your leading article on "Shoes and Feet" (*Journal*, February 13, p. 488) dealing with the relationship of footwear to deformities, after 35 years' experience of fitting children's feet I can help you with one reason why these feet become deformed at an early age. It is because parents are unaware of the rate at which children's feet develop, and invariably when they are brought to us to have a new pair fitted their toes are at the end, and in many cases they have been restricted and are already beginning to be deformed.

Obituary

S. A. HENRY, M.D., F.R.C.P., F.R.C.S., D.P.H.

Dr. S. A. Henry, formerly medical inspector of factories and an authority on industrial diseases, died at his home in London on February 12.

Sydney Alexander Henry was born in Rochdale on August 15, 1880, the son of Dr. Joseph Henry. He was educated at Rossall School, Trinity College, Cambridge, and at St. Thomas's Hospital, qualifying in 1905. In the following year he graduated M.B., B.Ch.; he took the D.P.H. in 1908 and the D.T.M. of Liverpool in 1909; and in 1910 he proceeded M.D. After resident hospital appointments and postgraduate study he spent some years in practice in Rochdale, where he was appointed certifying surgeon under the Factories and Workshops Act. His particular interest in occupational health dated from this time, and he became an authority on the work of the certifying surgeon (now called the appointed factory doctor) not only from the aspect of the Factories Acts but also from that of the Workmen's Compensation Acts.

He was appointed a medical inspector of factories in the Factory Department of the Home Office in 1920, and his reputation as an authority on industrial disease was soon established. Industrial cancer was his special subject, and he became secretary of the departmental committee to investigate industrial causes of cancer of the scrotum, a subject on which he published a monograph in 1946. He was vice-president of the Section of Occupational Health at the Annual Meeting of the B.M.A. in 1929.

He had the rare distinction of being elected a Fellow of both Royal Colleges, becoming F.R.C.P. in 1945 and F.R.C.S. in 1952. He was twice Hunterian professor at the Royal College of Surgeons, where he and his sister founded the Joseph Henry lectureship in memory of their father. At the Royal College of Physicians he gave the Milroy lectures in 1943. In the following year he was Chadwick lecturer, choosing for his subject "Medical Supervision in Industry in Peace and War."

E. R. A. M. writes: Dr. S. A. Henry devoted himself to the study of industrial health, on which he became an international authority. Particularly noteworthy and of fundamental and enduring importance was his searching and most painstaking investigations of skin cancer. These he continued until within a few months of his last illness, to the great benefit of the data on this subject collected by the Factory Department.

In 1920 he was appointed H.M. Inspector of Factories (Home Office), the fourth to be so appointed. He was responsible under Sir Thomas Legge for the medical inspector's work of an enormous district stretching right across the northern part of the country from Manchester. This was a challenge to a man of his energy and well did he accept it. His knowledge of the conditions in the textile industries was profound, and he became secretary to the departmental committees on epitheliomatous ulceration among mule-spinners and also on dust in cotton cardrooms.

His activities were legion in the pursuit of his work, and much did he do in his modest and unobtrusive way to fill in gaps in the knowledge of trades diseases and to extend it. He had the greatest admiration for Sir Thomas Legge, and after the death of the latter he put together (at Sir Thomas's wish) Legge's book *Industrial Maladies*. Both of them were absent-minded if they were concentrating on some particular investigation, and the story is told that one day they set out to catch a train and became so involved in discussions that they never caught it that day.

A kindly erudite man, he was most helpful to his juniors, and an excellent teacher. He used to collect first editions, old furniture, and prints. Earlier in his career his rooms would be so crowded with books and papers that it was barely possible to get near enough to him to shake his hand.

In all he spent almost twenty-five years in the Factory Department, which until his last few years was attached to the Home Office, and increasingly his work and personality exerted more influence. His standards were extremely high; scrupulous in his choice of words, he was a searcher for absolute truth, and as an investigator he assumed that nothing was without cause. A pioneer of the most enviable kind, his achievements and happy memories of him will endure.

J. A. MANIFOLD, C.B., D.S.O., M.D., D.P.H.

Major-General J. A. Manifold, formerly Director of Hygiene at the War Office, died at his home at Felpham, Sussex, on February 27. He was 75 years of age.

John Alexander Manifold was born on December 12, 1884, and educated at George Watson's College, Edinburgh, and at Edinburgh University, where he graduated M.B., Ch.B. in 1907. He joined the R.A.M.C. two years later, winning the Montefiore prize and medal at the Royal Army Medical College. He served throughout the first world war in the Mediterranean area, Egypt, and East Africa, being twice mentioned in dispatches and awarded the D.S.O. In 1921 he was appointed assistant professor of pathology at the Royal Army Medical College, and a year or two later he took the D.P.H. Posted to India in 1924, he served there for twelve of the next fifteen years in appointments progressing from deputy assistant director of pathology at Poona to deputy director of hygiene and pathology at Army Headquarters. During his early years in India he was the first to show, in the face of general scepticism in that country, that bacillary infection, and not amoebic infection as previously believed, was the major cause of dysentery there as elsewhere. He published his findings in 1928 and was instrumental in reorganizing laboratories and laboratory training, with the result that the diagnosis of cases of dysentery was greatly improved and the way was prepared for J. S. K. Boyd's work on the reclassification of known types and the identification of new types of dysentery bacilli. He was awarded the Leishman memorial prize and medal in 1928.

At the beginning of the second world war Manifold was appointed director of hygiene at the War Office and promoted major-general in 1941, becoming a deputy director of medical services. He proceeded to the degree of M.D. in 1942, was appointed C.B. in 1943, and served as Honorary Physician to the King from 1941 to 1944. Retiring from the Army after the war he became superintendent of St. Peter's Hospital, Chertsey. Five years later he finally gave up active professional work and for a number of years lived a country life in Essex, taking an active interest in village activities and giving practical encouragement to local sport: until the end of his life the people there looked upon him as a friend and adviser, though he spent his last six years at Felpham in Sussex.

During these last years he sustained great losses with the death of his two sons, as a result in each case of fatal injuries, and for the three years before he died he suffered a series of what, with a characteristic mixture of courage and impatience with forced inactivity, he called "idiotic cardiac attacks." To the last, however, he remained cheerful in the face of bereavement and illness, speaking of "defeating" each attack of the latter and continuing to take a keen interest in the Army and actively to assist the work of the British Legion on behalf of ex-Service men even from his sickbed.

John Manifold will be remembered as one of the most distinguished of Army medical officers. With his keen mind, strong convictions, and resolute nature he was impatient of stupidity, indecision, and lethargy. He loved justice, and the victim of what he considered unfair treatment found in him an active and ardent champion. His courage and kindliness and his cheerfulness in adversity were remarkable, and he will be sorely missed by his widow and daughters-in-law, to whom we offer our sympathy.—G. T. L. A.

LESLIE POWELL, M.B., B.Ch.

Dr. Leslie Powell, consulting aural surgeon at the Royal Berkshire Hospital, Reading, died at his home at Woodley, near Reading, after a short illness on January 22. He was 76 years of age.

Born on November 19, 1883, Leslie Powell spent most of his early years in Reigate. He was educated at Rugby, King's College, Cambridge, and the London Hospital, qualifying in 1910. He held a number of house appointments at the London, and graduated M.B., B.Ch. in 1911. He came to practise in Reading in 1915 in partnership with Dr. Roberts and Dr. House. At that time, apart from his interest in otolaryngology, he was surgeon to the Reading War Hospital. After the first world war he gave up general practice and was appointed ear, nose, and throat surgeon to the Royal Berkshire Hospital. During the ensuing years he founded and built up the large E.N.T. department, from which he retired in 1948.

A keen member of the Sections of Otology and Laryngology at the Royal Society of Medicine, he served on the council of the Section of Otology from 1928 to 1930, and was secretary to the Section in 1930–1. At the Annual Meeting of the B.M.A. at Oxford in 1936 he was vice-president of the Section of Oto-rhino-laryngology.

Dr. Powell was fond of sport, being a member of the Vine and South Berks Hunts. In addition he was a first-class tennis player and at one time captained the Berkshire team. Golf was one of his favourite pastimes, and he was often to be seen on the Sonning golf course until his failing strength compelled him to confine his attention to the less strenuous activity of gardening. He is survived by his widow, two sons, and a daughter.

G. W. DRYLAND, M.B., B.Ch.

Dr. G. W. Dryland, who practised in Kington, Herefordshire, died suddenly on February 2 while driving home after work. He was 78 years of age.

Gilbert Winter Dryland was born at Kettering on December 29, 1881, the son of Dr. J. W. Dryland (and the younger brother of Dr. L. W. Dryland, who also practised in Kettering). He was educated at Uppingham, Caius College, Cambridge, and Guy's Hospital. After qualifying in 1907 he was house-surgeon to the late Sir William Arbuthnot Lane. Shortly after he left Guy's he entered practice in Kington, in 1909, and remained in the same practice for the rest of his life.

Appointed to the staff of the Kington Cottage Hospital, he administered many thousands of anaesthetics there. He was also medical officer to the infirmary and held many public offices. He was commissioned in the R.A.M.C. in 1915, but was invalided out eighteen months later and returned to his practice, also looking after a Red Cross hospital. He graduated M.B., Ch.B. at Cambridge in 1916. In the second world war he served with the Home Guard, and trained his ambulance squads to a high state of efficiency.

He represented the Hereford Division of the B.M.A. and the local medical committee at many important conferences, and was chairman of the Herefordshire Division of the B.M.A. in 1923 and president of the Hereford and Worcester Branch the following year. Later he was a member of the Herefordshire executive council. After he retired from active practice, he worked for the Ministry of Health as a regional medical officer: this gave him great satisfaction, as he was able to keep in touch with other practitioners and patients.

While at Cambridge he started the University hockey league and later played for Guy's and the United Hospitals teams. He was a keen tennis-player until a coronary attack five years ago forced him to stop. From his student days he always looked forward to his annual holiday sailing on the Norfolk Broads. When he first went to Kington he started the first troop of Boy Scouts there, and was scoutmaster for some years.

He took a great interest in all the activities of the little town in which he lived. He will be long remembered, and greatly missed by the people of Kington, who have for many years regarded him as a friend and counsellor as well as doctor. His very human and kindly attitude endeared him to everyone.

Dr. Dryland is survived by a widow and a daughter.

K. WALLER TODD, M.R.C.S., L.R.C.P., D.T.M.

Dr. K. Waller Todd died suddenly on February 5, on his way from work to his home in Clapham. He was 59.

Kenneth Waller Todd qualified from the London Hospital in 1923, took the Diploma in Tropical Medicine in Brussels in 1926, and went with the Baptist Missionary Society to the Belgian Congo. From then until 1939 his work was in West Africa, with periods of service as college medical officer at Achimota, with the Methodist Mission in Sierra Leone, and with leper hospitals and the Church Missionary Society in Nigeria. He wrote a manual on first-aid in illness which has been published in French, Hausa, and Swahili. A pioneer in recognizing the hunger in Africa for books, he made it his continuing interest to see that it was met.

During the second world war he served in the R.A.M.C. from 1940 to 1946, and three and a half years of this was as a prisoner of war in Singapore, where he supported the health and morale of the other prisoners with fortitude and inspiration. In 1947 he returned to West Africa to carry out a survey for the National Association for Prevention of Tuberculosis. Later he went to Papua with the Kwato Mission. His last medical post was as assistant-director of public health (medical training), Papua and New Guinea.

Kenneth Todd had a gift of conversation and made warm and lasting friendships. In what were to prove his last few days he had spent time with his old "chief," the first principal of Achimota College, also an evening in the company of African leaders of many races from Kenya, Ghana, and South Africa. He was happiest to use his training to bring people of widely separated backgrounds together. Kenneth and his wife, who survives him, had ever a warm welcome in their home for their many overseas friends. He often expressed his gratitude for meeting the Oxford Group in 1933: he had a compelling faith, and the "Moral Re-Armament" of the nations was his mainspring.—L. C. M.

G. H. LUCAS, M.R.C.S., L.R.C.P.

Dr. G. H. Lucas, who practised for many years in the Isle of Ely, died at his home in Wisbech on February 6, at the age of 85.

George Humphrey Lucas was born at Uckfield, Sussex, on June 8, 1874, the eldest son of Dr. George Lucas, who was himself the son of a doctor. He was educated at Bedford Grammar School and the Middlesex Hospital medical school, qualifying in 1897. He began practice in Wisbech in 1903, at first in partnership with the late Dr. H. C. Meacock and afterwards on his own, and he was on the medical staff of the North Cambridgeshire Hospital for 45 years. He did not retire until September, 1957, when he was 83 years of age and had been in practice for 54 years.

Dr. Lucas gave long service not only to his patients but also to his fellow-doctors. He was chairman of the Isle of Ely local medical committee for 28 years, and still held that office at the time of his death; he was also chairman of the Isle of Ely executive council (and its predecessor the insurance committee) for a total of 18 years; and he held appointments at one time or another on very many other committees. He was held in high esteem by his professional colleagues, as was shown in tangible form by a presentation

to him shortly before he retired, and by the fact that he was elected to the chairmanship of the Isle of Ely Division of the B.M.A. 40 years ago.

His life-long hobby was music, both choral and orchestral, especially in connexion with his church, to which he was devoted. He was a churchwarden for 20 years, a member of the choir for 55 years, and he read the lessons regularly for 42 years. In short, Dr. Lucas led a long life of devoted service to his fellow-men, both professional and lay, and it will be very difficult, if not impossible, to fill the gap created by his passing. He leaves a widow, two sons, and a daughter, to all of whom our very sincere sympathy is extended.—C. T.

J. L. FARMER, M.B., Ch.B., D.P.H., D.Obst.R.C.O.G.

Dr. J. L. Farmer, medical officer of health of Winchester Rural District Council and senior medical officer for mental health services under the Hampshire County Council, died suddenly on February 8 at his home at Littleton, Hants, at the age of 46.

John Lumsden Farmer was born on August 7, 1913. He studied medicine at Glasgow University, graduating M.B., Ch.B. (with commendation) in 1936. After qualification he was for a time resident medical officer at Heathfield Infectious Diseases Hospital and Seafield Maternity Hospital, Ayr. He took the D.P.H. in 1939 and the D.Obst.R.C.O.G. in 1945. Before moving to Winchester in 1948 he was an assistant medical officer of health and assistant school medical officer under the Warwickshire County Council.

R. S. B. H. writes: "Johnny" Farmer was a man one took to right away, and to know him was to respect him and what he stood for. A most generous, kindly, and, above all, genuine person, I never heard him say a cross word to or about anyone. His charming smile and manner soon put his patients at their ease. He was a good doctor, interested in his work, especially for the mentally handicapped, a delightful colleague, and a very great personal friend. He seemed to enjoy life to the full and tackled anything he did with great zest, energy, and enthusiasm. Never sparing himself where others were concerned, he never seemed to tire and nothing was too much trouble for him. His sudden death at the age of 46 is a great blow to all of us who knew him, and he will be sadly missed. He was devoted to his work, and, above all, to his family. He leaves a widow and two daughters.

W. U. D. LONGFORD, L.R.C.P.&S.Ed.

Dr. W. U. D. Longford, who practised at Rainham, Kent, died suddenly at his home there on February 10. He was 68 years of age.

William Ulic Desmond Longford was born in London on June 22, 1891, and was educated at St. Paul's School and St. Bartholomew's Hospital, qualifying in 1917. After holding a resident appointment at his teaching hospital, he joined the R.A.M.C., and served in the Middle East for a period during and immediately after the first world war. After leaving the Army he held resident appointments at the General and Eye Hospital, Swansea, and the Seamen's Hospital, Greenwich, and from 1921 to 1922 was a ship surgeon in the Blue Funnel Line, visiting Japan, China, and the Philippine Islands. He entered general practice in Holywood, Co. Down, in 1925, where he remained for seven years before coming to Rainham in 1932.

A keen sportsman, he represented St. Paul's and Bart's as a heavyweight boxer, and in 1923 reached the semi-final of the Scottish sword championship. Genealogy was his chief hobby, and he was a member of the Irish Genealogical Research Society for many years, being the author of a publication in the Society's journal in 1956 entitled "The Fitzmaurices of Duagh." As a member of the B.M.A., he regularly attended the meetings of the Rochester, Chatham, and Gillingham Division and was chairman from 1952 to 1953. He was also Admiralty surgeon and agent, and Treasury medical officer, and for the past twelve years had been a member of the Kent and Canterbury local medical committee.

Desmond Longford will be remembered by his friends for his vitality and enthusiasm in all he did. He was, in every sense of the word, a family doctor; one in whom his patients could place their trust and confidence in the knowledge that their anxieties and fears would receive sympathetic understanding and kindly attention. Although aware of the nature of his cardiac disability, he always remained cheerful, and, in spite of the physical strain imposed upon him, was able to maintain to the end the same high standard of medical efficiency with which one always associated the conduct of his practice. He will be deeply missed by many who had great affection for him.

Dr. Longford is survived by his widow, a daughter, and three sons, two of whom have followed him into the medical profession. The sympathy of his friends is extended to them.—G. O. S. R.

J. R. K. THOMSON, O.B.E., M.R.C.S., L.R.C.P.

Dr. J. R. K. Thomson died on February 16 at his home in Penrith, Cumberland, where he had practised for over 30 years. He was 69 years of age.

James Robert Karran Thomson was born in Penrith on May 13, 1890, the eldest son of the late Dr. D. G. P. Thomson and elder brother of the late Dr. Douglas D. C. Thomson. He was educated at King William College, Isle of Man, and the London Hospital, qualifying in 1913. During his time at the London Hospital he won the Leatheby prize and he also played rugby football for his hospital and for the Eastern Counties. After qualification he held resident appointments at the London Hospital, and, having joined the R.A.M.C. in 1915, he saw service in a cavalry field ambulance throughout Allenby's Palestine campaign. Twice mentioned in dispatches, he was later appointed O.B.E. In 1919 he returned to Penrith and took over the practice at Bishops Yard which had formerly belonged to his father, who had died some years previously. He was chairman of the Cumberland Division of the B.M.A. from 1935 to 1936 and was a member of the old County panel committee. In 1937 he became county controller of the Cumberland and Westmorland V.A.D., and during the second world war he held the rank of major in the Home Guard.

Dr. Thomson had many interests outside medicine. A keen follower of the Ullswater Fell Fox Hounds, he was joint master from 1934 until 1940. He was chairman and later president of the Penrith Branch of the British Legion, chairman of the local branch of the Antiquarian and Archeological Society, and president of the Westmorland Conservative Association from 1957 until last year, when he resigned for reasons of ill-health. He was an acknowledged expert on the history and enunciation of the Cumbrian dialect.

"Dr. Jim," as he was locally known, was a popular and successful country practitioner, having the trust and esteem of his patients. His success was due primarily to his care, astuteness, and sound clinical judgment. After retiring he took a great interest in the activities of the district with his customary enthusiasm, charm, and humour. He lived a full life, and will be greatly missed by many friends.

He leaves a widow, a son, and a daughter, with whom the warmest sympathy will be felt.—K. T.

R. G. ANDERSON, M.D., D.P.M.

Dr. R. G. Anderson, a Lord Chancellor's Visitor in Lunacy and formerly a commissioner of the Board of Control, died after a short illness on February 12 at the age of 60.

Rupert George Anderson was a student at Edinburgh University, where he graduated M.B., Ch.B. in 1924, proceeding M.D. eight years later. Early in his medical

life he took the D.P.M. and joined the mental hospital service of the London County Council, in which he had a successful career, becoming deputy medical superintendent of Horton Hospital. He left this post in 1938 to become a commissioner of the Board of Control. The war interrupted his career, for in 1940 he joined the R.A.M.C. and served as a lieutenant-colonel in a psychiatric hospital in the Middle East. In 1953, some years after his return to Britain, he became a Lord Chancellor's Visitor in Lunacy, a post which entailed much travelling. His unmistakable sincerity and integrity must have brought comfort to innumerable patients and to their distressed relatives.

In his work he was conscientious almost to a fault and would placidly undertake any task, no matter how arduous or uncongenial. He endeared himself to all he met. His modest and unassuming manner was apt to disguise what was an alert and able mind. He had a very keen sense of humour and a fund of quiet wit, together with a remarkable gift of mimicry, which, however, was never anything but kindly. He was "Andy" to all his many friends, who will miss him sorely.

His death at such a comparatively early age seems all the more unexpected and tragic because of the fact that he had never had a day's illness, apart from one attack of pneumonia. He leaves a widow, a son, and two daughters.

JOHN DOCKRAY, M.B., F.R.C.P.

Dr. John Dockray, physician to the Royal Isle of Wight County Hospital, Ryde, died in that hospital on February 21. He was 59 years of age.

John Dockray was born at Carnforth, Lancashire, on September 17, 1900. From the Lancaster Royal Grammar School he won a scholarship to Trinity College, Cambridge, completing his clinical training at St. Bartholomew's Hospital. Qualifying in 1925, he graduated M.B., B.Ch. in 1928, and took the M.R.C.P. in 1930. After qualification he became house-physician to Lord Horder, and later held the posts of house-surgeon at Addenbrooke's Hospital, Cambridge, and resident medical officer at the Royal Chest Hospital, London. About this time, too, he spent six months as medical adviser to the Crown Prince of Siam.

In 1931 he became a general practitioner in the Isle of Wight, being appointed consulting physician to the Royal Isle of Wight County Hospital two years later. Chairman of the Isle of Wight Division of the B.M.A. in 1943, he played an important part in the organization of the hospital services in the Island after the National Health Service came into being. He was chairman of the medical advisory committee to the Isle of Wight group of hospitals and later a member of the South-west Metropolitan Regional Hospital Board.

A physician of outstanding ability, Dr. Dockray was elected F.R.C.P. in 1950.

F. H. writes: By those of us who were at Bart's with John Dockray he is remembered as one of Horder's young men—one of those who by reason of their special qualities merited Lord Horder's special attention. Those who knew him as a colleague and as a friend during the twenty-nine years that he lived and worked in the Island have seen the fulfilment of his early promise. His example must profoundly affect those who have had the privilege of working with him. He was a great physician but an even greater doctor. His first consideration was the welfare of his patients, and he worked at all hours on their behalf. He leaves a widow, to whom we extend our heartfelt sympathy in her great loss.

Dr. L. FIRMAN-EDWARDS writes: The medical profession in the Isle of Wight has sustained a sad loss in the unexpected death of John Dockray, who was loved, trusted, and respected by all who knew him. I had the privilege of working with him as a colleague on the medical staff of the Royal Isle of Wight County Hospital from 1937 and of the Isle of Wight group hospitals until my retirement in 1958. Throughout that time, and indeed since, he was a model of what a physician should be—kind, courteous, and patient, of sound judgment and knowledge, and dedicated to his work. It is not often that a physician working in a somewhat remote area is elected by the Fellows of the Royal College of Physicians to their number, but the fact that John Dockray was so elected is a tribute to the esteem in which he was held by the College. We shall surely miss him.

Sir ROBERT HUTCHISON, Bt., M.D., LL.D.
F.R.C.P., Hon.F.R.C.P.Ed.

The obituary of Sir Robert Hutchison was published in the *Journal* of February 20 (p. 571).

R. C. H. writes: Sir Robert Hutchison was a great figure in our profession. I remember calling him out in consultation about 50 years ago, and during a discussion about student days in Edinburgh a reference to his own brilliant record there elicited a confession that he did not get a medal in physics. The winning of a medal in every other subject, in the face of the enormous competition, at least numerical, of Edinburgh's very large classes, is surely evidence of a most unusual all-round mental capacity. As to his wit, which so many enjoyed and which sometimes had an edge, I remember that in Canada in 1930, during the B.M.A. tour of that magnificent country, he said in a public address that "vegetarianism is a dietetic creed which fills its devotees with wind and self-righteousness."

Sir CHARLTON BRISCOE, Bt., M.D., F.R.C.P.

The obituary of Sir Charlton Briscoe was published in the *B.M.J.* of March 5 (p. 733).

We are indebted to Dr. J. L. LIVINGSTONE for the following appreciation: Sir Charlton was an extremely sound general physician at a time when the diagnosis was made at the bedside with little help from the laboratory and *x*-ray department. His thorough yet rapid examination of a case was a joy to watch, and he was kindly and human in his dealings with the patient. More interested in research than in clinical teaching, he would sometimes spend forty minutes recording the tone and contractions of each intercostal muscle: he might suddenly become aware of the waiting students, and would then give a brilliant clinical talk with a few shrewd questions which kept the students on their toes. He was particularly interested in the mechanism of respiration, and used to share a private laboratory with Dr. Arthur Whitfield and Sir Lenthal Cheatle where the three would meet and arguments would range, and often rage, over a wide field of medical and surgical topics, the chances of the hospital XV, or the politics of the day.

As chairman of the medical committee and a member of the committee of management for many years, he did much service to King's. He was a founder member of the Hospital Lodge and was treasurer for many years. He had a busy private practice and was loved by his patients, many of whom were relatives of his colleagues on the staff.

He had been senior physician for some six years when a major operation at the age of 61 made him resign his hospital appointments at the height of his powers. He had always had a love of the country with an interest in farming, and he was a good shot. He had a country house at Lakenheath with some hundreds of acres of heathland, and he devoted his energies to making this rather barren soil productive.

He never lost touch with the hospital, and when well over 80 would attend meetings of the Lodge, and he rarely missed the annual hospital dinner, where he was always surrounded by a crowd of his old students obviously delighted to see him. Sir Charlton represented the traditions of King's, and all recognized his essential honesty and probity. He inspired affection and was loved by everyone.

Medical Notes in Parliament

PUBLIC HEALTH LABORATORY SERVICE

The Lords have completed their revision of the Public Health Laboratory Service Bill, and sent it to the Commons. The principal change has been that made in the constitution of the board which is to administer the service. As originally drafted, the board was to consist of a chairman and nine other members of whom two (one being the chairman) were to be fully registered medical practitioners, two members appointed after consultation with the Medical Research Council, two bacteriologists, two medical officers of health, and two members with administrative experience. The limit of 10 members has been removed, and the board is now to consist of a chairman (appointed, as before, by the Minister, but not necessarily a doctor); not fewer than two persons appointed after consultation with the M.R.C.; not fewer than two bacteriologists; not fewer than two medical officers of health; and—new representations—at least one person appointed after consultation with "such organizations as appear to the Minister to represent the hospital service," and at least one fully registered medical practitioner engaged in general practice, appointed after consultation with "such organizations as the Minister recognizes as representative of practitioners so engaged."

Viscount HAILSHAM, Lord Privy Seal, acknowledged that these changes were designed to meet the views expressed by Lord Taylor. They ensured representation of the interests concerned as users of the service, of the Medical Research Council, and of the branch of the profession providing the service. The minimum legal number of members would be eight, although the minimum intended was nine, but the Minister would be able to appoint others if he thought it desirable. The chairman would not necessarily be a member of the medical profession, and it was quite possible that the Minister would sometimes appoint a layman. The actual composition of the board would depend on the results of the Minister of Health's consultations with the various bodies concerned.

QUESTIONS IN THE COMMONS

Training for Mentally Handicapped Children

Mr. N. DODDS (Erith and Crayford, Lab.) asked the Prime Minister on March 3 if he would direct the Ministries of Education, Health, and Labour to appoint a joint committee to review as a matter of urgency the scales of provision being made by various local authorities for the education and training—including industrial training—of all classes of mentally handicapped children and adolescents, whether capable of receiving formal education or not. Mr. H. MACMILLAN replied that he was informed that local authorities were developing their education and training services for the mentally handicapped both by increasing provision and improving standards. Although all were aware that there is still a good deal to be done in this field, the other Ministers and he did not see the need for such a committee.

Mr. DODDS asked if the Prime Minister appreciated that what was asked for in this question was asked for by the National Society for Mentally Handicapped Children. The help accorded to the mentally handicapped varied considerably from one district to another. Because of the suffering entailed, by children and parents alike, was it not incumbent upon the Government to see that the best possible facilities were available to them, wherever they lived? Mr. MACMILLAN said the booklet recently published* was brought to his attention. It was a question of whether this particular piece of machinery was a wise one. At the same time, they must recognize that a great deal of work had been done in recent years. Work on the provision of further places in the schools' building programme was going on; special courses for teachers had been established, and more courses were starting in autumn, and for those handicapped children unsuitable for education at school provision by the local authorities had been greatly increased in recent years. An additional 40 such schools had been provided in the last two years. The Government would certainly do their best, and he would study the booklet referred to, at which he had already glanced.

Mr. M. STEWART (Fulham, Lab.) said that owing to the widely different practices of different local authorities and the number of different Government departments concerned it was difficult to get a clear picture of where the nation as a whole stood on this question, and consequently it was difficult to say exactly on what lines they ought to proceed in future to get the best results. Might not an inquiry of this kind be able to do for these children what they hoped the advice of the Crowther Committee would do for normal children? Mr. MACMILLAN replied that there had been an inquiry by a Royal Commission, which reported as short a time ago as 1957. It was just a question of whether this particular piece of internal machinery was a good one or not. He could assure the House that they would do their best, by whatever machinery was available, to press on with this problem.

Education and Training of the Mentally Handicapped Child, 1960. National Society for Mentally Handicapped Children, 162a, Strand, London, W.C.2. Price 1s. 3d. (post free).

Rubber Foot and Ankle

Mr. LESLIE LEVER (Manchester, Ardwick, Lab.) asked the Minister of Health whether he was aware that a rubber foot-and-ankle unit had been widely available on artificial limbs issued in Germany since 1949; and what steps he proposed to ensure that British limbs maintained their high standards and kept in line with tested improvements and developments obtained in other countries. Miss EDITH PITT, Parliamentary Secretary, stated on March 3 that the Minister knew that a unit of this type had been in limited use in Germany. A rubber foot-and-ankle unit was available on limbs supplied in this country, and experiments were going on with foreign units of this kind and a German unit had been ordered for comparison. The Ministry's officers, through visits to foreign centres and their association with international organizations and with national organizations in other countries, were in touch with the major proved developments abroad in the design and methods of manufacture of limbs, and foreign components were tested by the research department at Roehampton with a view to incorporating any proved beneficial features in British limbs.

Limb-fitting in London

Mr. LEVER also called attention to the substantial overloading of the facilities for limb-fitting and repairs at Roehampton; and asked what proposals the Minister had for the creation of additional limb and appliance centres so as to achieve a more personal and clinical approach to the individual problems of limb-fitting. Miss PITT told him that the Minister was considering whether an additional limb-fitting centre should be established in the London area.

Charge for Doctors' Telephone Calls

Mr. L. PAVITT (Willesden, West, Lab.) asked the Postmaster-General on March 2 if he would exempt the local telephone calls of general practitioners to hospitals from the revision of rates, which proposed that such calls would be on a timed basis for charging purposes. Mr. J. R. BEVINS said that no doubt Mr. Pavitt had in mind the subscriber trunk-dialling tariff under which all calls would be charged for in units of 2d., the amount of time so bought depending on the distance. With this system, many local calls would be charged 2d. instead of 3d. He was afraid it was technically impossible to exempt, from timing, local calls from or to particular installations.

Mr. PAVITT asked him to look again at the technical difficulties. There was a precedent in that other emergency calls were exempt from payment. The new proposal would place a terrific burden on general practitioners in trying to

place people in hospitals. They often needed to ring three or four hospitals, and they could not ask a hospital to ring back. He suggested that the difficulties could be adjusted on the accounting system, even if the calls were originally timed. Mr. BEVINS said that he appreciated the peculiar position of doctors under the new system, but he was advised that the technical difficulties of making this differentiation were insuperable. He was, however, willing to have a look at it again. Mr. GEORGE BROWN (Belper, Lab.) protested that doctors were not the only people who used their telephones for social services calls—there were M.P.s, trade union officials, and others. Mr. BEVINS told him that the case of doctors was a special one, as they often had to wait for connexions to hospital wards.

Shrewsbury Inquiry

Mr. ELLIS SMITH (Stoke-on-Trent, South, Lab.) asked the Minister of Health on February 29 what correspondence he had received from the Shrewsbury Trades Council about alleged irregularities in charges made under the Health Service since July, 1955; what replies he had made; what were the terms of reference of the inquiry appointed by him; and to what extent were the Trades Council consulted about the kind of investigations to be made.

Mr. D. WALKER-SMITH replied that he had received two letters. He had invited the council to make available to the regional hospital board any facts in their possession which might help the board in the preparation of their statement of case to the committee of inquiry. This they had declined to do. The terms of reference were:

"To inquire in accordance with Section 70 of the National Health Service Act, 1946, into allegations of irregularities in charging National Health Service patients for medical services in the Shrewsbury area and in particular the allegation that £25 had been paid with a view to procuring admission to a maternity bed at a hospital in Shropshire and to report to the Minister on the facts found."

The Trades Council were not consulted.

Mr. ELLIS SMITH asked what representation the Minister had received about the inquiry being held in private; what advice was submitted by the regional hospital board; what requests he received from the medical consultants within the Shrewsbury area that the inquiry should be held in public; and if an open public inquiry would now be held. Mr. WALKER-SMITH said he had received representations on behalf of individual medical practitioners and from the Trades Council. The Regional Hospital Board had accepted his decision that the inquiry should be held in private.

Oral Contraceptives

Mr. SYDNEY IRVING (Dartford, Lab.) asked the Minister of Health on March 7 whether he was satisfied that experimental tests with oral contraceptives being carried out in certain parts of the country were being properly controlled and were safe. Mr. WALKER-SMITH: Limited clinical trials of oral contraceptives are being carried out in this country through unofficial channels, but my information is that they are being carried out under medical supervision and that adequate precautions are being taken for the safety of those participating.

Artificial Insemination

Dr. A. D. D. BROUGHTON (Batley and Morley, Lab.) asked the Minister what was his estimate of the number of children born annually in England and Wales as a result of the practice of artificial insemination. Miss PITT said they had no information on which to form a satisfactory estimate. A committee on artificial insemination, appointed by the Home Secretary and Secretary of State for Scotland, was engaged in studying this matter, and might be expected to review whatever information was available.

Arsenite Spray on Potatoes

Mrs. J. BUTLER (Wood Green, Lab.) asked the Minister of Agriculture, Fisheries and Food whether he was satisfied that no danger to public health would result from the arsenite spraying of potato foliage on this year's crop. Mr. J. GODBER, the Parliamentary Secretary, replied that by voluntary agreement the use of alkali arsenites would cease after the 1960 potato harvest. Surveys had shown that potatoes from crops treated with alkali arsenites did not contain residues dangerous to consumers. The main risk was to operators and to cattle, but he was confident that those concerned would exercise the most stringent safety precautions in this final season of use and that the extra period would be of great value for the commercial development of suitable substitutes.

Flour Improvers Inquiry

Mr. N. DODDS (Erith and Crayford, Lab.) asked what progress had been made by the preservatives subcommittee of the Food Standards Committee carrying out a study of substances and processes for bleaching or improving the maturing of flour. Mr. GODBER replied that the subcommittee had made an extensive study of this subject, and were now taking evidence from trade interests before completing their report.

Medico-Legal

DOCTOR'S RIGHT TO USE HIS CLINICAL JUDGMENT

[FROM OUR LEGAL CORRESPONDENT]

The father of a pupil at the Nautical College, Pangbourne, failed in an action brought on behalf of his dead son, Peter Lightly Holland, against the Devitt and Moore Nautical College, Ltd., and the college's medical officer, Dr. Clifford Thomas (*The Times*, March 4). Mr. Justice Streatfeild delivered judgment for the defendants in the Queen's Bench Division on March 3.

Clinical History

Peter Holland was born in 1938 and from the age of three suffered from mild epileptic attacks which had gradually improved. In 1952 he entered the Nautical College, where, in 1954, he contracted infective hepatitis. Dr. Thomas saw him on May 24, noted that his stools were pale and his urine dark, and diagnosed a mild case of this disease. He put him on a fat-free diet with glucose and confined him to bed. The patient had a normal appetite, did not suffer from nausea or vomiting, and said he felt perfectly well. His condition improved so that he was allowed to get up in his room. He was told that if he continued to improve he would be allowed to go home for the mid-term week-end on June 5. In saying this, Dr. Thomas was influenced by the fact that the boy was a potential epileptic and would be heartbroken if not allowed to go home, with possible effects on his epileptic condition. By June 4 the patient was not completely improved, but he was nevertheless allowed to go home.

The journey home was a very tiring one, occurring on the Whitsuntide holiday week-end, and involved a walk of a mile with a suitcase to the station and difficult conditions on the trains and the London Underground. However, when he returned to college and reported to the sick bay he was very cheerful although slightly jaundiced. He was told to resume his studies, but to return to the sick bay to eat and sleep. The following day he had a relapse, on June 29 he went to hospital, and in 1957 he died from cirrhosis of the liver. This action was started in 1956.

College Liable on Prospectus

The first question decided by the court was the responsibility of the college authorities. Assuming that the doctor had been negligent, was the college responsible?

The general rule is that one is vicariously liable for acts done in the course of employment by one's servant, but not for such acts done by an independent contractor. The difference between servant and independent contractor is often expressed as the difference between a contract *of* service and a contract *for* services. One is liable for injuries caused by one's chauffeur, but not for injuries caused by one's taxi-driver. However, in cases concerning the liability of a hospital for its doctors, the courts have in many cases been able to avoid this difficult distinction by finding that the hospital authority itself undertook a duty of care towards the patient: the hospital did not discharge this duty simply by providing a reasonably competent staff; the duty was only discharged if reasonably careful and proper treatment was given.

In the present case the college's medical officer received an annual fee of £260 plus the N.H.S. capitation fees for the boys and the staff for his part-time duties. It was argued by the defence that this was a contract *for* services and not a contract *of* services. The court avoided deciding this point by holding that the college in its prospectus, which formed part of the contract between parents and the college, had held itself out as providing medical attention in addition to education, the medical attention being covered by fees which were stated to include treatment in the sick bay. Treatment in the sick bay was not limited to treatment by the sister. Therefore, if Dr. Thomas had been negligent, the college would be liable.

Textbooks Not Final

But had the doctor been negligent? The case against him was that he had let his patient out of bed too soon, had treated the case too lightly as a mild one, and had departed from orthodox treatment. His answer was that the treatment was prescribed with the individual needs of the patient as a potential epileptic in mind.

Mr. Justice Streatfeild stated first the well-established principle that a doctor is not expected to be a miracle-worker but only to show the diligence, skill, and knowledge to be reasonably expected of an ordinary practitioner. He then referred to the matter of departing from orthodox treatment. If one particular textbook were to be followed slavishly, he said, no doctor could escape liability unless he kept his patient in bed until all signs of bile pigment disappeared from the urine and stools. Mr. Justice Streatfeild made it quite clear that, although a practitioner must be guided by the general standards of medical learning of his time, he must not be frightened to depart from the "textbook treatment" in proper cases. As *The Times* reports it:

> "Textbook writers, or writers of articles, were writing of a subject generally. They were not writing of a particular patient and it was common ground between all the doctors that something must be left to the judgment of the doctor on the spot, who did not have to treat a case of infective hepatitis only, but had a particular patient, Peter Holland, to treat. Dr. Thomas had to bear the whole picture in mind. A general practitioner was entitled to use his common sense, his experience, and his judgment so far as it fitted the particular case. It would be a sorry day for the medical profession if it were said that no doctor or surgeon ought to depart one tittle from that which he saw written in the textbooks. Indeed, one might go the other way and say that if a doctor did not do so he might be negligent."

In the court's opinion, not only was there no negligence in this case, but there had been no mistake at the first stage.

FRAUDULENT HYPNOTIST

[FROM OUR LEGAL CORRESPONDENT]

In the Coventry County Court on February 12 a married woman obtained an order for the return of £53 paid as fees to a hypnotist, Victor Vinmar, of Upper Fitzwilliam Street, Dublin (*Birmingham Post*, February 13). The judge stigmatized the treatment given for nervous disorder as bogus, and the conduct of the treatment highly suspect. The plaintiff, who first met Vinmar as a result of an advertisement he had placed in a local paper, said that he assaulted her, and vainly tried to induce her to remove her clothes while she was under hypnosis. Vinmar did not defend the action or appear.

Universities and Colleges

UNIVERSITY OF OXFORD

Dr. John Badenoch, Director of Clinical Studies, has been appointed representative of the University on the council of St. Luke's Homes Ltd., until February 18, 1961, in place of Dr. F. G. Hobson, who has resigned.

The board of the Faculty of Medicine has co-opted Dr. A. M. Cooke for the statutory period of two years from the first day of Hilary Term, 1960.

UNIVERSITY OF CAMBRIDGE

Dr. E. H. R. Ford has been appointed a University Lecturer in the Department of Anatomy for three years from October 1, 1960, and the Hon. R. H. Adrian, M.B., B.Chir., a University Lecturer in the Department of Physiology for three years from January 1, 1961.

In Congregation on February 6 the degree of M.B. was conferred, by proxy, on D. M. C. Forster.

Dr. Marthe L. Vogt, F.R.S., has been elected into a Supernumerary Fellowship of Girton College, with tenure from April 1, 1960.

UNIVERSITY OF ABERDEEN

The following appointments are announced: Dr. A. H. C. Sinclair-Gieben, as Senior Lecturer in Mental Health; Dr. N. G. Fraser, as Lecturer in Mental Health; and Dr. John Findlay, to a Terminable Lectureship in Anatomy.

UNIVERSITY OF EDINBURGH

Dr. R. H. Girdwood, Reader in the Department of Medicine, has been admitted to membership of the Faculty of Medicine.

Dr. E. A. Harris has resigned his appointment as Lecturer in the Department of Medicine.

UNIVERSITY OF LONDON

Dr. Hermann Lehmann, Senior Lecturer in Chemical Pathology at St. Bartholomew's Hospital Medical College, has been appointed to the University Readership in Chemical Pathology tenable at that College.

The title of Reader in Chemical Pathology in the University has been conferred on Dr. G. R. Webster in respect of his post at Guy's Hospital Medical School.

UNIVERSITY OF BIRMINGHAM

Professor C. F. V. Smout has been appointed representative of the university on the governing bodies of Prince Henry's Grammar School and Prince Henry's Exhibition Foundation, Evesham.

The title of University Research Fellow has been given to the following during the tenure of their present awards on appointments or for the period of their stay in the University: Dr. E. Marley (Nuffield Research Fellow), in the Department of Experimental Psychiatry, and Dr. C. Chlouverakis, Dr. Margaret T. England (Endowment Fund Research Fellow in the Department of Medicine), Dr. M. G. Fitzgerald (Endowment Fund Research Fellow in the General Hospital, Birmingham), Dr. C. T. Flear (Beit Research Fellow), Dr. D. J. Fone (Research Associate in the General Hospital, Birmingham), Dr. W. A. Hudson and Dr. Annette B. Rawson (Senior Registrars, Queen Elizabeth Hospital, Birmingham), Dr. D. J. O'Sullivan (Senior Registrar, General Hospital, Birmingham), and Dr. H. C. White (Senior Registrar in the Department of Psychological Medicine, United Birmingham Hospitals), all in the Department of Medicine.

The following appointments are announced: Sir Arthur Thomson, Senior Fellow in Medical History, from January 1, 1960; Dr. R. F. Fletcher, Lecturer in the Department of Medicine, from October 1, 1960; Dr. J. D. Blainey, part-time Lecturer in the Department of Experimental Pathology (Metabolic Diseases) for the period he holds his present post of Consultant Physician to the United Birmingham Hospitals; Mr. N. E. Winstone, temporary Lecturer in the Department of Surgery, from December 1, 1959, to September 30, 1960; Mr. J. A. Williams, Lecturer in the Department of Surgery, from October 1,

1960; Dr. H. G. Clarke, temporary Lecturer in the Department of Physiology, from January 1 to December 31, 1960.

Mr. G. T. Watts, Lecturer in Surgery, resigned from his appointment on February 14, 1960.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on February 11, with Sir James Paterson Ross, President, in the chair, Professor John Bruce, President of the Royal College of Surgeons of Edinburgh, was admitted to the Honorary Fellowship. Professor Carl Semb, of Oslo, was elected to the Honorary Fellowship.

Sir Cecil Wakeley and Sir Harry Platt (Past Presidents), Sir Zachary Cope, Mr. W. A. Innes, and Mr. C. R. Coleman were elected Members of the Court of Patrons.

Dr. Cuthbert Dukes was appointed the Thomas Vicary Lecturer for 1960.

A Hunterian Professorship was awarded to Mr. P. M. Weston, of the West Indies.

Dr. Bertram Cohen was appointed the first Nuffield Research Professor of Dental Science in the College, and Dr. G. V. R. Born Vandervell Professor of Pharmacology.

The following were elected to the Fellowship *ad eundem*: Isabella Forshall, P. G. Cutlack Martin, G. E. Moloney, A. W. Kay.

The Honorary Medal of the College was awarded to Sir Cecil Wakeley, Past President.

The Hallett Prize was awarded to J. C. Doyle, of the University of Melbourne, and Miss I. S. S. Rajah, of the University of Ceylon. Handcock Prizes were awarded to Stephen Jeremy McDonald, of Charing Cross Hospital Medical School, and to David Robert Harvey, of Guy's Hospital Medical School.

Diplomas of Fellowship in the Faculty of Anaesthetists were granted as follows:

K. W. Dodd, G. B. Burchell, I. M. Brown, T. K. Hardy, N. H. Eve, M. R. Milne, W. Braude, W. S. Dykes, J. N. Thorpe, I. W. Davidson, S. R. Umrigar, R. D. McC. Davie, N. H. Jafry, P. W. McCormick, Mary F. West, Catherine K. Adam, G. Clarke, D. T. McClements, Marie M. Simpson, W. I. Colbeck, Winifred E. Elesh, C. J. R. Elliott, J. P. N. Hicks, A. B. Lodge, W. N. C. McCleery, N. McLeod, D. D. Moir, E. D. T. Ross, P. A. Tsoi-A-Sue, D. M. Davies, G. C. Fisk, Dorothy E. Harris, D. D. Hart, P. I. W. Knell, I. M. J. Mair, R. R. Manning, Isobel Speirs, L. T. Wijeyaratne, F. B. N. Clarke, A. T. R. Fuller, C. F. Hider, B. A. Lyder, Maung U Win, J. H. Stevens, T. H. Taylor, R. J. G. Thomson.

Diplomas in Medical Radiotherapy were granted, jointly with the Royal College of Physicians of London, to D. S. Andrew and K. D. Reddy.

ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

The following have been elected office-bearers of the College from May 25, 1960, to 1962: *President*, Dr. T. M. Greenaway; *Vice-Presidents*, Dr. F. R. Home, Dr. H. M. Rennie, Dr. E. H. Roche; *Censor-in-Chief*, Dr. K. B. Noad; *Honorary Treasurer*, Dr. G. B. D. Hall; *Honorary Secretary*, Dr. L. Harris.

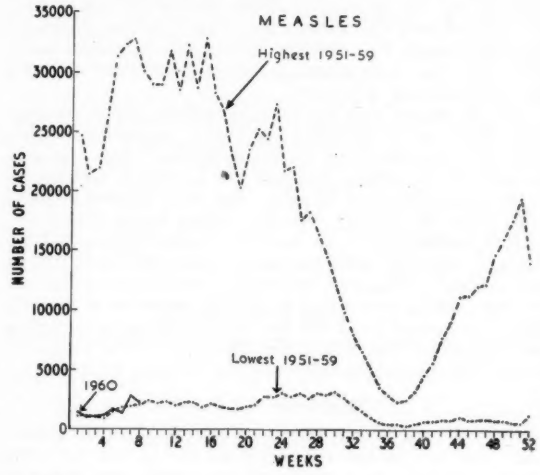
Vital Statistics

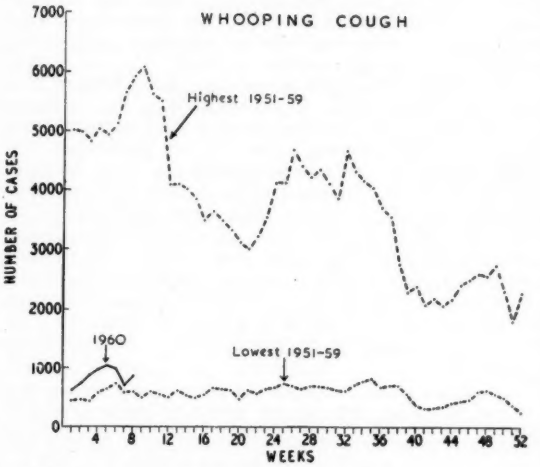
Diphtheria in Belgium

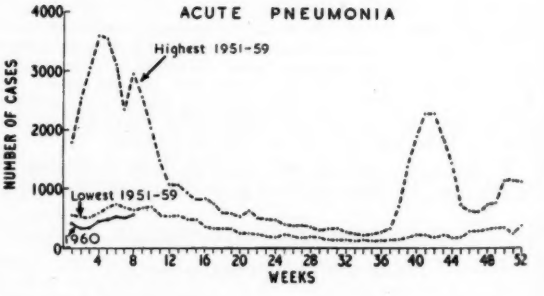
A rise in the incidence and mortality of diphtheria was experienced by most European countries during the early years of the second world war. In Belgium the number of cases rose steadily from 2,311 in 1940 to a maximum of 16,157 in 1943, and the number of deaths increased from 403 to 892. The incidence then fell, notifications reaching a minimum of 512 cases in 1951, with 53 deaths. In subsequent years the number of notifications increased, and over 600 cases were notified annually in the four years 1953–6, although the mortality fell and only 20 deaths were registered in 1956. In 1957 a further rise in incidence occurred, 879 cases being notified, and in 1958 the figure went up to 1,312. There were 45 deaths in 1957 and 34 in 1958. The numbers of children immunized have fluctuated considerably, the totals for the three years 1956–8 being 31,688, 77,584 and 53,809. In the various areas of the country there have been large annual variations in the numbers immunized—e.g., in Limbourg 12,990 children were immunized in 1955 but only 470 in 1958. In a letter to members of the medical profession the Minister of Health of the Belgian Government has expressed concern about the rise in notification of diphtheria and has stressed the need for immunization (*Arch. Belges Méd. soc.*, 1959, **17**, 671).

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







Influenza in England and Wales

There is no laboratory or other evidence that influenza is prevalent in Britain. During the week ended February 27 the number of deaths in England and Wales from influenza (56) was a little higher than in the previous week (42). The

notifications of pneumonia (550), death from pneumonia (820), and deaths from bronchitis (895) were also all in excess of the previous week's figures, and there was a moderate increase in the new claims to sickness benefit.

Venereal Diseases

In England and Wales during the quarter ending February 29, 1960, 960 new cases of syphilis were reported as attending the clinics, as compared with 1,032 the previous year. Of these, 205 were classified as primary, secondary, or latent in the first year of infection. 5 cases of congenital syphilis in children aged under 1 year were reported, and 83 cases in persons over that age. New cases of gonorrhoea (with corresponding 1959 figures in parentheses) numbered 9,224 (7,986), of chancroid 57 (65), and of non-gonococcal urethritis (males only) 5,952 (5,197).

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in January was 72 compared with 93 in the previous month, and 82 in January, 1959.

The number of cases of industrial diseases in the United Kingdom reported during January were as follows: lead poisoning 3, arsenical poisoning 1, compressed air illness 1, epitheliomatous ulceration 4, chrome ulceration 21; total 30. There were no deaths.

Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Feb. 20	Week Ending **Feb. 27**
Measles		
Kent	150	**209**
Ashford U.D.	71	**94**
Dover M.B.	60	**55**
Lancashire	408	**459**
Blackpool C.B.	58	**52**
Liverpool C.B.	141	**78**
Manchester C.B.	36	**62**
Meningococcal Infection		
Warwickshire	3	**9**
Birmingham C.B.	2	**9**
Dysentery		
Cheshire	21	**74**
Wallasey C.B.	4	**10**
Macclesfield R.D.	0	**25**
Essex	106	**107**
Romford M.B.	21	**55**
Saffron Walden M.B.	26	**17**
Gloucestershire	36	**50**
Bristol C.B.	30	**43**
Hampshire	3	**25**
Gosport M.B.	0	**12**
Lancashire	459	**458**
Blackpool C.B.	4	**28**
Oldham C.B.	80	**98**
Preston C.B.	28	**28**
Swinton and Pendlebury M.B.	48	**37**
Walton-le-Dale U.D.	0	**24**
Middlesex	84	**93**
Edmonton M.B.	33	**33**
Enfield M.B.	20	**35**
Norfolk	51	**66**
Norwich C.B.	11	**38**
Monmouthshire	25	**51**
Abercarn U.D.	0	**42**
Glasgow	113	**103**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **February 20** (No. 7) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	5	1	1	0	4	2	0	3	0	1
Dysentery	1,646	200	290	17	3	1,193	78	110	19	9
Encephalitis, acute	0	0		0		3	0		0	
Enteric fever:										
Typhoid	3	2	0	0		4	1	0	0	1
Paratyphoid	3	0	0	0		6	1	2(B)	0	
Food-poisoning	175	29	4	0		107	22	3	0	
Infective enteritis or diarrhoea under 2 years	-			10	13				7	31
Measles*	2,083	47	34	4	39	26,464	1561	918	648	1073
Meningococcal infection	20	1	4	1	3	27	2	13	1	3
Ophthalmia neonatorum	12	0	1	0		19	1	3	0	
Pneumonia†	480	43	253	5	4	2,339	265	764	10	9
Poliomyelitis, acute:										
Paralytic	5	1	0	0	3	10	0	1	1	
Non-paralytic	3	0	2			2	0	3		
Puerperal fever§	185	23	7	1		265	53	12	1	
Scarlet fever	1,200	34	109	30	27	1,245	62	87	39	20
Tuberculosis:										
Respiratory	498	62	76	15		462	43	96	22	
Non-respiratory	77	8	13	2		47	6	5	3	
Whooping-cough	778	58	181	2	49	575	25	92	70	168

DEATHS	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	1	0	0	0	0	0	0	0	0	0
Dysentery	1	0		0		1	0		0	
Encephalitis, acute		1			0		0			0
Enteric fever	0		0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	9	0	1	0	0	8	0	1	0	2
Influenza	42	5	1	0	2	1,121	147	27	0	3
Measles		0	0	0	0		1	0	0	
Meningococcal infection		0	0				1	0		
Pneumonia	716	74	31	21	8	1,951	259	99	25	10
Poliomyelitis, acute	0	0		0	0	4	0		0	0
Scarlet fever		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	88	5	6	0	2	134	8	11	3	3
Non-respiratory		1	0	0	0		3	0	0	0
Whooping-cough	0		0	0	0	0	0	0	0	0
Deaths 0–1 year	367	36		10	5	392	35	36	8	8
Deaths (excluding stillbirths)	11,880	934	712	161	196	17,143	1815	1023	153	200
LIVE BIRTHS	15,492	1312	1019	249	332	14,809	1235	1012	250	288
STILLBIRTHS	350	23	26			346	26	25		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Queen's Doctors Honoured

Mr. J. H. PEEL and Dr. V. F. HALL, who attended the birth of Her Majesty's third child, have received appointments in the Royal Victorian Order. Mr. Peel becomes K.C.V.O. and Mr. Hall C.V.O.

Wolfson Endows Royal Society Chair

The Isaac Wolfson Foundation has offered £200,000 to the Royal Society for the endowment of a research professorship to be known as the Wolfson Research Professorship of the Royal Society.

The Chair—appropriately endowed at the beginning of the Society's tercentenary year—will be held by a distinguished British scientist who will devote the whole of his time to research in such fields as the President and Council of the Royal Society may think fit. The first holder, who has yet to be appointed, will work in the physical sciences or their borderlines with biology.

Dangerous Oil-heaters

The three million drip-feed radiant oil-heaters now in use in Great Britain can cause serious fires very quickly indeed if they are placed in a draught, such as that coming from an open window or outside door, and the Department of Scientific and Industrial Research advises that the greatest care should be taken to avoid placing them in such positions. This advice follows the publication of a report by the Joint Fire Research Organization (*Effect of Draughts on the Burning of Portable Oil Heaters*, H.M.S.O., price 1s. 3d. net).

As a result, Mr. R. A. BUTLER, the Home Secretary, has announced that the Government are to begin consultations immediately with a view to adopting a safe standard of performance for this type of heater, and to deciding whether such heaters already on the market should be withdrawn from sale and modified.

Review of Accident Services.—The following organizations (with their representatives so far notified) are taking part in the Accident Services Review Committee, details of which are given in an annotation at page 792:

Royal College of Surgeons of England (Professor F. A. R. STAMMERS, Mr. F. W. HOLDSWORTH, Mr. J. C. BARRETT). Royal College of Surgeons of Edinburgh (Professor D. M. DOUGLAS, Mr. D. MCINTOSH). Royal College of Surgeons of Ireland (Mr. D. W. MONTGOMERY, Mr. G. I. FENTON). Royal Faculty of Physicians and Surgeons of Glasgow (Professor R. BARNES, Mr. R. B. WRIGHT). Royal College of Physicians of London (Dr. E. N. ALLOTT). College of General Practitioners (Dr. R. COVE-SMITH, Dr. J. FRY, Dr. J. H. HUNT). British Medical Association (Mr. A. M. A. MOORE, Mr. R. ROAF, Mr. H. OSMOND-CLARKE, Mr. H. H. LANGSTON). Society of British Neurological Surgeons (Mr. W. S. LEWIN, Mr. G. F. ROWBOTHAM). Society of Thoracic Surgeons of Great Britain and Ireland. British Association of Plastic Surgeons (Mr. P. H. JAYES, Mr. R. MOWLEM). British Orthopaedic Association (Mr. H. J. SEDDON, Mr. N. CAPENER, Mr. W. GISSANE, Mr. J. C. SCOTT).

B.M.A. Film Competition

The winners of the British Medical Association's 1959 competition for 16mm. medical films are:

Commercial category: First prize: "Bronchial Carcinoma" (colour, sound, 30 min.), Dr. C. H. C. Toussaint, and N. P. Schenker, for Pfizer Ltd.; *awards of merit*, "The Sully Concept of Primary Pulmonary Tuberculosis" (colour, sound, 45 min.), the Sully Hospital, Penarth, and Film Surveys, Ltd., for Pfizer Ltd.; and "Tendon Free Grafting" (colour, sound, 17 min.), Mr. P. W. Brand and Ciba Laboratories, Ltd. *Non-commercial category:* No prize or awards of merit were given in this category, but the film "Marlborough House" (colour, sound, 12 min.), Department of Health, City and County of Bristol, and Bristol Cine Society for Marlborough House Parent-Teachers Association, received a special commendation for a film judged not to be a medical film for the purposes of the competition.

Manchester Medical Society

Dr. H. LEMPERT'S presidential address to the Pathology Section of the Manchester Medical Society on February 10 concerned "Treatment Control and the Pathologist."

He said that while there was general agreement on the definition of the science of pathology there were many misconceptions concerning the role of the pathologist. At one time a pathologist could supervise the work in all four main divisions of pathology—histopathology, bacteriology, biochemistry, and haematology. New developments in recent years had necessitated the appointment of a pathologist for each division of the subject. So rapid were these developments that further subdivisions could be envisaged. During the past decade the number of tests at the department of clinical pathology at the Manchester Royal Infirmary had doubled. Not only were the tests of diagnostic value, but they were becoming increasingly valuable in therapy or control of treatment. It seemed proper for medically qualified people to be in charge of laboratories carrying out tests the results of which could affect a patient's life.

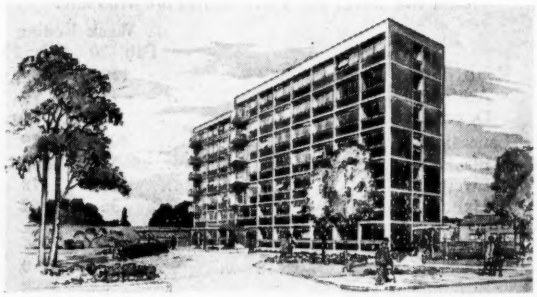
Association of Industrial Medical Officers

With the object of encouraging further interest and research among its members, the Association of Industrial Medical Officers is offering a prize of 50 guineas for the best original entry in essay form on any subject within the field of occupational health. All members of the A.I.M.O. are eligible to compete for the prize, which will be awarded in 1961. Full details are obtainable from the Honorary Secretary of the A.I.M.O., 47, Lincoln's Inn Fields, London, W.C.2.

Housing for the Old in Birmingham

Birmingham Welfare Committee has planned a new kind of multi-story home for old people, on Swedish lines. It will be built on a one-acre site in Perry Barr and is designed to overcome the acute shortage of building land in the city.

The building will house 76 old people, but each floor—reached by slow-moving lifts—will be a separate unit for groups of about 14 people, with their own "bed-sitters," lounges, dining-rooms, and bathrooms. The residential staff will live on the top floor



[Birmingham Post and Mail

and there will be an emergency day-and-night call system. The cost—£1,346 a bed—compares with £1,266 a bed for a more conventional old people's home in the Yardley district.

"Russian Review of Biology"

An English translation of *Russian Review of Biology*, a publication of the Academy of Sciences of the U.S.S.R., is now being published six times a year for the Institute of Biology, with the support of the Department of Scientific and Industrial Research. The Institute hopes that it will enable English-speaking biologists to follow recent biological research in the Soviet Union. The English editor is Professor H. MUNRO FOX, F.R.S. The subscription rates, net and post free, are £9 ($30) for the first nine issues, including those of 1960, and thereafter £6 10s. ($20) a year. Further details may be obtained from the publishers, Oliver and Boyd, Ltd., Tweeddale Court, 14, High Street, Edinburgh, 1.

Care of Old People

In its *Twelfth Annual Report* for the year ended September 30, 1959, the National Corporation for the Care of Old People draws attention to how little is being done to provide the elderly with suitable housing, and asks that more thought should be given to planning to meet future housing needs.

Grants have been made during the year to a number of different kinds of projects, including some research into geriatric nursing

problems and the provision of home lifts in several voluntary homes for old people. A study was also started just after the end of the year to assess the true place in the social services of the experimental rest homes run by the Corporation. The great majority of the Corporation's grants to voluntary committees providing chiropody services to the aged have ceased, and the Governors comment on the future of the service, which can now be operated by local authorities. The report ends with a general plea for a better understanding of the needs of old age, for more knowledge by the general public of the services which exist to help the old, and with an expression of regret at a tendency to bring old people's welfare into the field of party politics at both local and national levels.

"Journal of the Singapore Paediatric Society"

The proceedings of the Singapore Paediatric Society were produced in duplicated form from 1952 to 1958. They have now been replaced by the biannual *Journal of the Singapore Paediatric Society*. This will continue to record the Society's activities, but its scope has been enlarged to include progress in paediatrics and child health in Singapore, Malaya, and the neighbouring countries. The editor is Dr. WONG HOCK BOON, and manuscripts should be sent to him at the Paediatric Unit, General Hospital, Singapore, 3. Subscription inquiries are dealt with by the publishers: Papineau Studios Advertising, 22a and 24a, Clemenceau House, Clemenceau Avenue, Singapore.

British Red Cross Society

The British Red Cross Society would be grateful if anyone who has finished with his *British Medical Journal* would pass it on to the Society, which in particular wishes to use illustrations from it for the benefit of lecturers and instructors. They should be sent to the British Red Cross Society, 6, Grosvenor Crescent, London, S.W.1.

Boat Race Tickets

Vitamins Limited have a limited number of tickets available for watching the Boat Race from their premises on April 2. These can be obtained by application to them at 23, Upper Mall, Hammersmith, London, W.6.

Agadir Disaster

A surgical team from the Welsh Regional Hospital board is to treat victims of the earthquake at Agadir. The members of the team are Mr. E. LEWIS, surgeon-in-charge of the plastic surgery centre, St. Lawrence Hospital, Chepstow, Mr. M. N. TEMPEST, his senior registrar; and Mr. H. G. MIDDLETON, anaesthetist. (*The Times*, March 3.)

COMING EVENTS

Glasgow University and R.F.P.S.—Clinical teaching ward rounds for postgraduate students. For details see *Journal*, advertisement p. 66.

Willesden General Hospital Medical Society.—Mr. A. DICKSON WRIGHT: "Some Momentous Operations." March 16, 8.30 p.m., Department of Physical Medicine, Willesden General Hospital, Harlesden Road, London, N.W.1.

Ileostomy Association of Great Britain, London Division.—Dr. I. MARTIN SCOTT: "The Prevention and Treatment of Soreness of the Skin," March 19, 2.15 p.m., Great Hall, B.M.A. House, Tavistock Square, London, W.C.1. Exhibition of appliances; tea (2s. 6d. a head).

Association of Clinical Biochemists: Biochemical Society.—Symposium: "Formation and Breakdown of Haemoglobin," March 26, 11 a.m., lecture theatre D, School of Chemistry, The University, Leeds, 2.

British Council for Rehabilitation: University of St. Andrews.—Three-day residential course: "Rehabilitation, Its Industrial and Social Implications," March 29–31, Queen's College, Dundee. Details from General Secretary, British Council for Rehabilitation, Tavistock House (South), Tavistock Square, London, W.C.1. (EUS 4037–8.)

Glasgow University and R.F.P.S.—Conference on "The Kidney," March 30 to April 1. For details see *Journal* advertisement p. 67.

Association of Surgeons of Great Britain and Ireland.—Annual Meeting, Birmingham, April 7–9. Details from the Association, 47, Lincoln's Inn Fields, London, W.C.2.

C.M.F./M.E.F. Physicians' Dinner.—Simpson's-in-the-Strand, April 9, with Dr. E. R. BOLAND in the chair. Details from Dr. A. WILLCOX, 59, Harley Street, London, W.1.

International Seminar on Health Education.—London, April 19–22. Special sessions will be devoted to problems of health education in undeveloped countries. Details from Central Council for Health Education, Tavistock House North, Tavistock Square, London, W.C.1.

B.M.S.A. Conference on Tropical Medicine.—Liverpool, April 20–23. Details from British Medical Students' Association, B.M.A. House, Tavistock Square, London, W.C.1. Forty students can be accepted, those from tropical countries receiving preference.

Institute of Accident Surgery.—Inaugural Ruscoe Clarke Memorial Lecture: "The Care of the Injured," by Sir ALEXANDER DRUMMOND (Director-General of Army Medical Services), April 25, 5.30 p.m., University of Birmingham. Admission free, by ticket from the secretary, Institute of Accident Surgery, The Accident Hospital, Bath Row, Birmingham, 15.

Edinburgh Postgraduate Board for Medicine.—One-week course: "Surgical Aspects of Road Accidents," Edinburgh, June 13–17. For details see *Journal* advertisement p. 66.

NEW ISSUES

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

BRITISH JOURNAL OF INDUSTRIAL MEDICINE.—Issued quarterly (£3 annually). The new issue (Vol. 17, No. 1) includes:

A Clinical and Environmental Study of Byssinosis in the Lancashire Cotton Industry. S. A. Roach and R. S. F. Schilling
A Survey of Small Factories. Margot Jefferys and C. H. Wood.
Studies in the Nature of Silicosis: A Suggested Mechanism of Fibrogenesis. P. F. Holt and C. W. Went.
Changes in the Lung Lipids of Rabbits and Guinea-pigs Exposed to the Inhalation of Silica Dust. C. S. Marks and L. W. Marasas.
Drug Treatment of Experimental Silicosis. Dinah M. James, T. G. Morris, and J. Marks.
A Comparison of the Emotional Stability of Coal-miners and Railwaymen. Judith S. Lion.
The Development of Rotary Nystagmus in the Cat as a Function of Age. N. E. Loveless.
A Study of Heat Stress in Extremely Hot Environments, and the Infra-red Reflectance of Some Potential Shielding Materials. Charles E. Lewis, Richard F. Scherberger, and Franklin A. Miller.
Excretion of Tricholoroethylene Metabolites in Human Urine. B. Souček and D. Vlachová.
Ecological Considerations on Nickel Dermatitis. Poul V. Marcussen.
Renal Lesions in Experimental Cadmium Poisoning. J. A. Bonnell, J. H. Ross, and E. King.
Two New Medical Centres.

JOURNAL OF CLINICAL PATHOLOGY.—Issued bi-monthly (£4 annually). The new issue (Vol. 15, No. 1) includes:

Generalized Cytomegalic Inclusion-body Disease Associated with Pneumocystis Pneumonia in Adults. W. St. C. Symmers.
Clinical and Pathological Findings in Ochronosis. Loyd R. Wagner, James L. Knott, Reginald A. MacHaffie, and John R. Walsh.
The Pathology of Asthma, with Special Reference to Changes in the Bronchial Mucosa. M. S. Dunnill.
A Case of Cerebral Mucormycosis Diagnosed in Life, with Eventual Recovery. Augustin Muresan.
The Total White Cell Count of the Blood as an Indicator of Acute Radiation Damage and Its Value During the First Few Hours after Exposure. E. V. Hulse.
The Toxicity of Rubbers and Plastics Used in Transfusion-giving Sets. C. D. N. Cruickshank, Caroline Hooper, H. B. M. Lewis, and J. D. B. MacDougall.
Penicillin Antibody. G. W. G. Bird.
The Bacteriology of Urinary Infections in Paraplegia. T. G. Scott.
The Biological Significance of the Anomalous Serum and Urinary Proteins of Myelomatosis, Lymphoma, and Other Conditions. J. A. Owen and C. Got.
Caeruloplasmin as Demonstrated by Starch Gel Electrophoresis. J. N. Cumings and C. J. Earl.
Flocculation Tests in Hydatid Disease. A. Fischman.
The Investigation of Lipoproteins in Lymph and Other Body Fluids by Paper Electrophoresis. W. G. Dangerfield, Elspeth B. Smith, J. B. Kinmonth, and G. W. Taylor.
True Glucose Content of Lumbar and Ventricular Cerebrospinal Fluid. Vincent Marks.
Standard Barium Sulphate Suspensions. J. F. Boyd and J. W. Sommerville.
Technical Methods: Photographic Recording of Precipitin Bands in Agar Gel. G. W. R. Dike.
Obituary: R. B. H. Gradwohl.

BRITISH JOURNAL OF OPHTHALMOLOGY.—Issued monthly (£6 annually). The new issue (Vol. 44, No. 1) includes:

Ocular Complications in Sickle-Cell Haemoglobin C Disease. Stewart Munro and Colin Walker.
Subconjunctival Administration of Soframycin in the Treatment of Corneal Infections. D. Ainslie and J. E. Cairns.
Some Biochemical Changes in Naphthalene Cataract. D. Salmony.
Diffuse Infiltrating Retinoblastoma. P. B. Schofield.
Intra-Ocular Gnathostomiasis. Ko Gyi.
Injection Technique for Studying Retinal Blood Vessels. H. R. Hausler and T. M. Sibay.
Iris Hole following Concussion Injury. J. D. Abrams.
Paralysis of Accommodation with Recovery after 5 Years. R. W. Stephenson.
Secondary Glaucoma after Occlusion of the Central Retinal Artery. J. S. Gupta.
Metastatic Carcinoma of Choroid. D. Stenhouse Stewart.
Patwardhan's Cross-Action Iris Retractor. D. G. Patwardhan.
Apparatus for the Diagnosis and Recording of Diplopia. E. C. Cowan.
Correspondence.
Book Review.
Notes.

BRITISH JOURNAL OF PREVENTIVE AND SOCIAL MEDICINE.—Issued quarterly (£3 annually). The new issue (Vol. 13, No. 4) includes:

Statistical Analysis of Suicide and Other Mortality Rates of Students. R. G. Carpenter.
Variability in Answers to a Questionnaire on Respiratory Symptoms. A. S. Fairbairn, C. H. Wood, and C. M. Fletcher.
Respiratory Tuberculosis in the Birmingham Region. P. G. Arblaster, K. W. Cross, and V. H. Springett.
Geographical Distribution of Disease. G. M. Howe.
Bronchitis in the Insured Population of Northern Ireland. C. W. Kidd and A. T. Park.
Social Class Distribution of Respiratory Tuberculosis Notifications in Northern Ireland, 1949-53. J. D. Merrett.
Secular Pattern of Congenital Oesophageal Atresia. G. Knox.
Index, 1959.

BRITISH JOURNAL OF VENEREAL DISEASES.—Issued quarterly (£3 annually). The new issue (Vol. 35, No. 4) includes:

Reactions to Antibiotics. R. R. Willcox.
Genital Neoplasms. C. D. Collins.
Treatment of Non-gonococcal Urethritis with Sigmamycin. W. Leach.
Neuropathological Findings in a Case of Juvenile General Paresis Treated with Penicillin. R. M. Norman, H. Urich, and W. A. Heaton-Ward.
Serological Tests in Long-standing Congenital Syphilis. J. Eng.
Studies of the Incidence of T. Pallidum Immobilizing Antibody in Rabbit Immune Sera against Various Types of Micro-organisms and Viruses. H. A. Nielsen and M. Metzger.
Female Consorts of Men with Non-gonococcal Urethritis. N. Rosedale.
Treatment of Gonorrhoea with P.A.M. and Probenecid. A. L. Hilton.
Treatment of Non-gonococcal Urethritis. G. Jelinek.
Treatment of Male Gonorrhoea with a Chlortetracycline-Sulphonamide Combination. G. M. Thomson.
Increasing Failure Rate After Using the Same Preparation and Dosage of Penicillin in the Treatment of Gonorrhoea. H. Giessing.
Synnematin B in the Treatment of Syphilis and Gonorrhoea. B. Schwimmer and N. D. Henderson.
Donovanosis Treated with Erythromycin Parenterally. S. Ghosh and R. Ghosh.
Treatment of Non-specific Urethritis with Tri-acetyl-oleandomycin (Evramycin) Parenterally. G. W. Csonka.
Treatment of Non-gonococcal Urethritis with Tri-acetyl-oleandomycin. R. R. Willcox.
Studies of Granuloma Inguinale. IV. J. Goldberg.
Mucocoele of Male Urethra. J. O. Doyle.
Chief Medical Officer's Report for 1958.
Index for 1959.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, March 14

GUY'S HOSPITAL.—At Physiology Theatre, 5.30 p.m., endocrine demonstration. Dr. G. A. Thomas: Disorders of Testicular Function.
INSTITUTE OF NEUROLOGY.—5.30 p.m., Professor D. Denny-Brown (Boston, U.S.A.): Nature of Brief Recurrent Cerebrovascular Episodes.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor E. Zaimis: Neurochemical Pharmacology.

Tuesday, March 15

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-1960.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Professor O. L. Zangwill: Asymmetry of Cerebral Hemisphere Function.
OSLER CLUB OF LONDON.—At National Hospital, Queen Square, W.C., 8.15 p.m., Dr. Macdonald Critchley: History of the Hospital and the Square.
SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, 8.30 p.m., Dr. G. T. Stewart: Fats in Food, Blood, and Arteries.
UNIVERSITY COLLEGE HOSPITAL MEDICAL SCHOOL.—4.30 p.m., Sydney Ringer Memorial Lecture by Professor M. Maizels: Salt and Water Balance in Cells.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. E. H. Larkin: Organic Dementia.

Wednesday, March 16

CHRISTIAN MEDICAL FELLOWSHIP.—At Royal Commonwealth Society, Northumberland Avenue, W.C. (Craven Street entrance), 8.15 p.m., Mr. Arnold S. Aldis: Keeping Faith with the Patient.
FACULTY OF ANAESTHETISTS: ROYAL COLLEGE OF SURGEONS OF ENGLAND.—4 p.m., Joseph Clover Lecture by Dr. J. A. Lee: Joseph Clover and the Contributions of Surgery to Anaesthesia.
HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.—8.15 p.m., Harveian Lecture by Professor J. Waldenström (Sweden): Aspects of Gamma Globulin Pathology.
INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. A. Tickner: Biochemistry of Psoriasis.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. Donald Barlow: Pathology, Treatment, and Complications of Achalasia.
INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. H. K. Vernon: Cancer of the Kidneys.
LISTERIAN SOCIETY.—At Lecture Theatre, King's College Hospital Medical School, 8.30 p.m., Presidential Address by Professor C. H. Gray.
MIDLAND MEDICAL SOCIETY.—At General Hospital, 8.15 p.m., clinical meeting.
ROYAL FREE HOSPITAL.—5.15 p.m. Dr. B. E. C. Nordin: Metabolic Bone Disease.
WILLESDEN GENERAL HOSPITAL MEDICAL SOCIETY.—At Department of Physical Medicine, 8.30 p.m., Mr. A. Dickson Wright: Some Momentous Operations.

Thursday, March 17

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., subject: Reduction of Radiation Hazards in the Use of Radium and Similar Sources. Papers by Dr. F. Ellis, Mr. R. E. Ellis, B.Sc., and Drs. N. G. Trott, Ph.D., and K. W. Taylor, Ph.D.
LIVERPOOL SOCIETY OF ANAESTHETISTS.—At Liverpool Medical Institution, 8 p.m., joint meeting with Liverpool Medical Institution. Symposium: Hypothermia in Cardiac Surgery. Speakers, Professor T. C. Gray, Dr. Charles McKendrick, Mr. L. J. Temple, Dr. J. C. Richardson, and Dr. I. C. Geddes.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Selby's, 6, Hanover Street, W., 6.45 p.m., annual dinner dance.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor A. E. Jones: Supervoltage *X*-ray Therapy of Intracranial Tumours.
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At Royal Army Medical College, Millbank, S.W., 7.30 p.m., laboratory meeting.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: postgraduate demonstration in psychiatry.
WEST LONDON MEDICO-CHIRURGICAL SOCIETY.—At Nurses' Hall, West London Hospital, 7.30 for 8 p.m., dinner meeting. Mr. P. D. Trevor-Roper: Influence of Eye Disease on Pictorial Art.

Friday, March 18

ANGLO-GERMAN MEDICAL SOCIETY.—At Ciba Foundation, 41, Portland Place, W., 8 p.m., annual general meeting.
INSTITUTE OF ALMONERS.—At William Beveridge Hall, Senate House, London University, W.C., 5.30 p.m., Dr. D. Stafford-Clark: The Doctor, the Patient, and the Public.
● INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. H. Meara: clinical demonstration.
INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. C. Batten: clinical demonstration.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Dr. Norman Hulbert: Vertigo—Differential Diagnosis.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. R. G. Pulvertaft: Advances in Hand Surgery. (2) 4 p.m., Dr. J. A. Fraser Roberts: Medical Genetics. VI.
SOCIETY OF CHEMICAL INDUSTRY: FINE CHEMICALS GROUP.—At School of Pharmacy, Brunswick Square, W.C., 6.30 p.m., joint meeting with Society for Analytical Chemistry. Mr. R. M. Pearson, A.R.I.C., and Dr. I. D. P. Wootton: Techniques of Automatic Analysis.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Durham.—On March 6, 1960, at Ryde Nursing-home, Isle of Wight, to Mabel (formerly Lewis), and Surgeon Commander P. D. A. Durham, R.N., a sister for Anthony and Jonathan—Katharine Eve.
Horton.—To Drs. Eric and Thalia Horton (by adoption) a son—Charles Richard.

DEATHS

Allan.—On February 11, 1960, at "Hillside," Beacon Lane, Grantham, Lincs, John Balfour Allan, M.B., Ch.B.Ed.
Anderson.—On February 12, 1960, in Birmingham, Rupert George Anderson, M.D., D.P.M., of 25, Coval Road, East Sheen, London, S.W.
Austin-Beveridge.—On February 6, 1960, at Bexhill, Helen Austin-Beveridge, M.B., B.S., of 13, Old Manor Close, Bexhill-on-Sea, Sussex.
Brodie.—On February 10, 1960, at Melbourne, Australia, Robert Charles Espinasse Brodie, F.R.C.S.Ed., F.R.A.C.P.
Eglinton.—On February 13, 1960, at Cranhill House, Street, Somerset, John Henry Cox Eglinton, L.M.S.S.A., aged 66.
Harland.—On February 10, 1960, at Foxdale, Isle of Man, George Blenkhorn Harland, M.D., D.P.H., late Indian Medical Service.
Henry.—On February 12, 1960, at 61, Overstrand Mansions, London, S.W., Sydney Alexander Henry, M.D., F.R.C.P., F.R.C.S., D.P.H., D.T.M.
Jones.—On February 9, 1960, at his home, Torryburn, Brompton Avenue, Rhos-on-Sea, Owen Thomas Jones, M.B.E., L.R.C.P.&S.Ed.
Longford.—On February 10, 1960, at his home, Rainham, Kent, William Ulic Desmond Longford, L.R.C.P.&S.
Morrison.—On February 8, 1960, at Lewis Hospital, Stornoway, Malcolm Falconer Morrison, M.B., Ch.B.Ed., D.T.M.&H., late of the Nigerian Colonial Medical Service.
Pandalai.—On February 5, 1960, Krishnan Gopinath Pandalai, F.R.C.S.
Parry.—On February 7, 1960, at Warwick, Peter Parry, M.B., Ch.B., aged 45.
Paterson.—On February 11, 1960, at Gorse Patch, Runfold, Farnham, Surrey, Surgeon Captain Adrian Charles Paterson, M.R.C.S., L.R.C.P.
Russell.—On February 12, 1960, at 34, Tooting Bec Gardens, London, S.W., Charles Mowbray Russell, M.B.E., M.B., Ch.B.
Taylor.—On February 15, 1960, at 17, Kent Terrace, London, N.W., James Maberley Taylor, M.R.C.S., L.R.C.P.
Thomson.—On February 10, 1960, at Westcroft, Dartford, Kent, David Maitland Thomson, M.B., B.S., aged 50.
Urquhart.—On February 8, 1960, at Denbigh, John Argyle Urquhart, M.B., Ch.B., D.P.H

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Pathogenic Organisms in Air

Q.—*When using multiple-dose injection phials, we are advised to inject an equal amount of air to facilitate withdrawal of the desired amount of solution or fluid from the ampoule. Does this contaminate the contents of the phial with pathogenic organisms?*

A.—It is true that hospital air may contain pathogenic organisms, but the number of staphylococci, for instance, does not often exceed 1 per cubic foot. This volume being 27 litres, and the volume of air usually injected into a phial being 1 ml., the operation might be carried out 27,000 times for every single occasion when one staphylococcus-containing particle was introduced. The second line of defence is the preservative, whether of phenolic or mercurial nature, in the injected material itself. This not only prevents growth, but is slowly lethal to any vegetative bacteria introduced into it. If it be assumed that a single infected particle can initiate infection, the material would be safer after the lapse of some hours than immediately, but the risk is obviously so remote that it can be disregarded.

Status Asthmaticus

Q.—*What is the domiciliary treatment of status asthmaticus in adults and children?*

A.—The present treatment consists basically in adrenaline subcutaneously, then intravenous aminophylline, followed by steroids, together with adequate fluids, an expectorant containing potassium iodide, and usually antibiotics. Death in status asthmaticus is not rare, especially in those aged over 30 and in all who have had previous dangerous status asthmaticus. Infants are also at risk. This must be borne in mind in considering the advisability of hospital treatment when adrenaline and aminophylline have failed, which in the writer's opinion is advisable for most patients. An "atmosphere" at home and inadequate nursing facilities are also in favour of hospital treatment. Constant attention is essential for those dangerously ill with status asthmaticus.

In adults adrenaline min. 5 (0.3 ml.), repeated in about 15 minutes, should be given, then 1 min. (0.06 ml.) per minute until a total of some 20 min. (1.2 ml.) or so have been given. If there is no improvement intravenous aminophylline 10 to 20 ml. (0.24 to 0.48 g.) should be given slowly over 10 to 15 minutes. In children the dose of aminophylline is 0.0003 to 0.006 g. per kg. of body weight given intravenously or rectally.[1]

The use of steroids is a notable advance in treatment. In adults[2] prednisone, 60 mg. in 24 hours, should be given by mouth for the first 24 hours, and if necessary for the next 24 hours, then 50 mg. in 24 hours, then 40 mg. in 24 hours for 24 or 48 hours, then 30 mg. in 24 hours for 24 or 48 hours, followed by 20 mg. per day. The dose is then reduced by 5 mg. every few days. The initial dose could be 40 mg. in 24 hours in less severe cases, while for intractable asthma, as distinct from status asthmaticus, 20 to 30 mg. is usually adequate. Intravenous prednisone, 25 to 100 mg., is given in addition in very severe cases during the first 12 to 24 hours. A gastric regime and avoidance of gastric irritants, such as aminophylline by mouth, is advisable in all cases, but in patients with a history of peptic ulceration the risks of death from status asthmaticus must be carefully weighed against the risk of haemorrhage or perforation. Steroids must be kept to a minimum and intravenous steroids used to supplement and reduce dosage by mouth.

The need for steroid therapy in children is less frequent. Glaser[1] recommends for status asthmaticus cortisone 50 to 75 mg. (prednisone 10 to 15 mg.) 8-hourly until the patient begins to respond (the response is usually in 6 to 18 hours, with an average of 8 hours); then every 12 hours for 24 hours, and then a reduction by 25 mg. or less every 8 hours. When a child is unable to take cortisone by mouth it is given intramuscularly. In two infants under 1 year the starting dose was 100 mg. intramuscularly and then 50 mg. 6-hourly. Levin[3] recommends for "severe asthma" in children over 5 years cortisone 25 mg. three or four times a day for one day, two doses of 25 mg. on the second day, one or two doses of 25 mg. on the third day, 25 mg. on the fourth day, and 12.5 mg. on the last day.

Oxygen is helpful in persistent severe asthma. Heavy sedation should not be used and morphine is contraindicated. Paraldehyde is the safest hypnotic. A history of penicillin allergy should be excluded before penicillin is given. Every effort should be made to prevent status asthmaticus by proper investigation of the asthma and treating attacks early and energetically.

REFERENCES

1 Glaser, J., *Allergy in Childhood*, 1956, pp. 252 and 253. Charles C. Thomas, Springfield, U.S.A.
2 Williams, D. A., in *Bronchial Asthma: A Symposium*, 1959, p. 52. Chest and Heart Association, London.
3 Levin, S. J., *Pediatrics*, 1955, **16**, 416.

Dullness and Epilepsy

Q.—*Epileptic pupils at a special school for educationally subnormal children are alleged to be unusually intellectually dull. Could this be due to the drugs they are taking, which include phenobarbitone, primidone, phenytoin sodium, and acetazolamide?*

A.—To answer the second part of this question first: phenobarbitone, primidone, or phenytoin sodium can all cause a dulling of the intellect, although most physicians treating epileptic children are agreeably surprised to find how slight this may be.

With regard to the allegation that epileptic children who are educationally subnormal are unusually dull, is this really true? A large group of epileptic children attending the National Hospital for Nervous Diseases, Queen Square, were found—curiously enough—by the Binet-Simon tests and a verbal test to have higher I.Q.s than the average.

Analgesic for Teething

Q.—*Would the application of an analgesic cream (such as lignocaine) benefit infants who are teething? Would there be any danger in this?*

A.—An analgesic jelly containing menthol for rubbing on the gums during teething has been on the market for many years and seems to afford some transient relief of pain. Ointments such as lignocaine, which contain a local anaesthetic, are not likely to have any ill effect unless used to excess, but their effect, if any at all, is equally transient. An oral analgesic such as aspirin 0.1 g., repeated not more often than three times in 24 hours, in occasional doses is probably as effective as anything.

Amplifying Foetal Heart Sounds

Q.—*What is the nature of the apparatus for amplifying foetal heart sounds, and what method is used for picking up the sounds?*

A.—Foetal heart sounds have a very low frequency and this makes their amplification and recording difficult and gives a poor signal-to-noise ratio. Hitherto most methods of detection have involved the use of a small microphone applied to the abdominal wall of the mother over the point of maximum intensity of the sounds, either by adhesive strapping, by elastic belt, or by use of a suction cup. None of these methods is satisfactory for more than about a quarter of an hour, and any displacement of the microphone weakens the reception and calls for tedious and troublesome readjustment. Even when a sufficiently strong signal has

been obtained, every extraneous noise is amplified with equally bewildering intensity, and a number of amplifiers using frequency attenuators have been produced to cut out all but the lowest and most relevant frequencies.[1] Attempts at monitoring the foetal heart rate are therefore often defeated by interference which the human ear is more skilled at disregarding than any known machine. For these reasons automatic foetal heart monitors have not lived up to the ingenuity of their design. A great improvement is the method developed in the Medical Physics Department, Edinburgh, by Simpson and Leask[2] and demonstrated by them at the scientific exhibition at the recent B.M.A./C.M.A Joint Annual Meeting. This method concentrates upon detecting the foetal heart sounds as mechanized vibrations and uses a vibrating arm whose natural frequency of vibration approximates to that of the foetal heart sounds —i.e., about 60 cycles per second. On the end of this arm is a grill through which a light is shone through another parallel and fixed grill on to a phototransistor. Further transistor amplification of the resulting signal is passed, after suitable modification, to a small loudspeaker. A reliable indication of the foetal heart is thus given, although the sounds are not truly reproduced. Because the pick-up is "deaf" to other frequencies it does not amplify extraneous noises and the signals can be used for fairly reliable monitoring of the foetal heart rate. This was demonstrated at the same exhibition with an elegant but robust mechanical recording system, and it is understood that the Edinburgh firm of Bruce Peebles are undertaking to produce it.

Foetal heart rate monitoring by picking up foetal electrocardiographic signals has proved considerably more difficult because of overshadowing by the maternal E.C.G. signals, skin currents, and extraneous interference.

REFERENCES
1 Taylor, S., and Fothergill, L., *Lancet*, 1956, **1**, 1050.
2 Simpson, D. C., and Leask, E., ibid., 1959, **1**, 1077.

Nasopharyngeal Infection and Midwifery

Q.—*What organisms are considered dangerous in the nose and throat of those who wish to do midwifery? What is the best method of elimination?*

A.—It is usual to examine only for haemolytic streptococci and to regard these as dangerous only if they are of Lancefield's Group A. Treatment depends on the site of carriage and its condition. Diffuse infection of the mucosa of the throat or nose is usually transient and in any case responds rapidly to treatment with penicillin: there is a form of chronic streptococcal rhinitis which may prove less amenable. When the site is the tonsil, and if it is hypertrophied, the streptococci are in deep crypts relatively inaccessible to penicillin, whether given systemically or applied locally, and they may reappear in time after even a vigorous course of treatment. Tonsillectomy may then be necessary: it will usually be judged to be advisable on general grounds.

Sodium Bicarbonate in Electrical Injuries

Q.—*One teaspoonful of sodium bicarbonate in ½ litre of water has been advocated in the first-aid treatment of those injured by high-voltage electric current. What are the modern views on this treatment?*

A.—Fröhlicher and Bull[1] advocate the early administration of sodium bicarbonate in the treatment of major destruction of the tissues by electricity, and they consider it to be a safe procedure for laymen to carry out. Fischer, Fröhlicher and Rossier[2] have described crush syndrome in such cases. Bywaters[3] recommends the hourly administration of sodium bicarbonate, 1 teaspoonful to the pint (0.6 l.) of water. Fröhlicher advises early alkalinization for two reasons. First, some of his patients died from renal failure some days after electrical accidents and he thinks they would have been saved by early administration of sodium bicarbonate, which could have been given by laymen. Secondly, he advocates conservative treatment, and he has obtained a surprising amount of restoration of function in individual cases. British surgeons, on the other hand, generally consider that the risk to life is too great and advocate early and complete resection of dead muscle.

REFERENCES
1 Fröhlicher, R., and Bull, A. S. E., *Transactions of the British Electrical and Allied Industries Research Association*, September and October, 1954.
2 Fischer, H., Fröhlicher, R., and Rossier, P. H., *Schweiz. med. Wschr.*, 1947, **77**, 826.
3 Bywaters, E. G. L., in *British Encyclopaedia of Medical Practice*, 2nd ed., vol. 4, p. 76. London.

Pruritus Vulvae

Q.—*What is the aetiology and treatment of pruritus vulvae in a nulliparous widow aged 39 who menstruates regularly and has no apparent local lesion? The urine is sugar-free and sterile, and she is mentally well adjusted.*

A.—Pruritus confined to the vulva is a symptom the basic cause of which must be found for treatment to be rational, for non-specific remedies such as *x*-rays and cortisone ointments have no lasting effect. Local examination should be repeated, and, in addition to further vaginal swabs to detect monilia, scrapings should be taken from the vulval skin to exclude a fungus infection. Although the urine has so far been free from sugar, a full glucose-tolerance test should be carried out, because, first, glycosuria may be present only when the blood-sugar level is high, and, secondly, pruritus may occur when there is hyperglycaemia without glycosuria. Achlorhydric anaemia is another cause of pruritus vulvae, so a full blood-examination is required and either a test for gastric acidity performed or a therapeutic test applied by giving acid. hydrochlor. dil. m. xv (1 ml.) with meals. Another possibility to be explored is an allergy to some local application (powder, soap, antiseptic) or even to the material or dye in the underwear. Finally, a psychogenic basis for the symptom is sometimes found, and further deeper questioning may show that this patient is not so well adjusted to her widowhood as stated.

Amphetamine with Phenobarbitone

Q.—*Would amphetamine or similar drugs counteract any tendency to sleepiness caused by phenobarbitone in the treatment of epileptic children?*

A.—Amphetamine—or preferably dextroamphetamine—is used as a routine by most neurologists to counteract any sleepiness due to phenobarbitone. Children (or adults) may find a dose of 2½ mg. adequate.

Correction.—We regret that the notifications of scarlet fever were incorrectly entered as deaths in the Table of Infectious Diseases and Vital Statistics published in the issue of February 27 (p. 661) and the notifications of measles as deaths in the Table published in the issue of March 5 (p. 739). There were no deaths from either of these diseases during the weeks in question.

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